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General Charles James Fox, M. D.
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TRANSACTIONS OF THE

SECTION ON

Practice of Medicine

of the
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at the Fifty-ninth Annual
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ANEURISM OF THE HEART.

WITH REPORT OF A CASE ASSOCIATED WITH MEDIASTINO-PERICARDITIS.

J. B. McELROY, M.D.
MEMPHIS, TENN.

Little space is given to the consideration of this subject in text-books on the principles and practice of medicine, or even in those on diseases of the heart. By the earlier medical writers the term "cardiac aneurism" was used to signify enlargement of the heart. Thus Auenbrugger and Corvisart used the terms "aneurysima activa," signifying enlargement from hypertrophy, and "aneurysima passiva," signifying enlargement with dilatation. Several years later John Hunter and his nephew Matthew Baillie, gave to the term its modern significance, viz., a partial dilatation of the cardiac wall; hence aneurism of the heart was often spoken of as partial aneurism.

In the general literature to-day three different conditions are spoken of under the term aneurism of the heart, namely:

1. Aneurismal dilatation of the coronary arteries, which may vary in size from a mustard-seed to a cherry, may be multiple or single, and is due to sclerosis or embolism of these vessels.

2. Aneurism of the valves of the heart, by which is meant a cavity in the substance of the valve, containing pus or other inflammatory products, clotted blood or débris. These arise from small areas of endocarditis, either on the surface or in the substance of the valve,

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and according to Drasche, who does not agree with some other authors, is more frequent in the mitral valve.

3. Aneurism of the cardiac wall.

The first two conditions are almost wholly of pathologic interest, but their inclusion under the term "aneurism of the heart" has somewhat confused the statistics on the subject.

It is to the third condition, or aneurism of the cardiac wall, that I shall refer in this paper. This is not of very frequent occurrence, as will be seen from the statement of Philip D. Bourland, who was able to find but two cases reported by American authors during thirteen years prior to 1904. In 1867 Pelvet collected reports of eighty-seven cases from the world's literature up to that time. In 1883 Legg made cardiac aneurism the subject of his Bradshaw lectures, in which he collected reports of ninety cases, probably including those of Pelvet. According to Warthin, more frequent reports of the condition have been made since that time, and there are now in the literature reports of possibly three hundred cases.

REPORT OF CASE.

Patient.—D. R., white, male, aged 49, was admitted to St. Joseph's Hospital, Dec. 24, 1907, to the service of Dr. W. T. Braun, to whose courtesy I am indebted for the privilege of observing the case. The patient complained of shortness of breath and dropsy.

Personal History.—Family history was negative. The patient had frequent attacks of malaria in Arkansas; also had grip, pneumonia and gonorrhea. He was kicked by a mule several years ago, losing the sight of his right eye. He had never had rheumatism and denied syphilis; had used alcoholic drinks moderately and had worked hard. About two years prior to this admission, he came to St. Joseph's Hospital complaining of shortness of breath and dropsy. According to the patient, after a prolonged stay, he returned home apparently well, and had no further trouble until a short time before his last admission.

Present Illness.—He had some pain in the chest, the location of which he was unable to define. It had not been severe,

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had not radiated to the side of the neck nor to the arm, and had not been associated with the fear of death. He had difficulty in getting his breath, especially on exertion, and at times the dyspnea had been so great as to require him to sleep sitting up. He had lately had some edema of the feet and ankles and had suffered with swelling and fulness of the abdomen.

Physical Examination.—The patient was a fairly well-nourished man. The skin was subicteric, the mucous membranes pale; there was a cataract in the right eye, slight edema of the feet and legs; no glandular enlargements.

Chest: There was dyspnea and slight impairment of respiratory expansion at the left base. There was a pulsating tumor in the chest wall, in the apex region. This pulsation seemed to be expansile and to correspond to the apex impulse. There was no systolic retraction in this area nor in the left back. There was some pulsation of the carotids, though not marked. The jugulars were not distended on deep inspiration and there was no diastolic collapse of these vessels. The peripheral veins were abnormally full. The abdomen was distended, but there was no distention of the abdominal veins.

Palpation: Vocal fremitus was possibly diminished over the left lower chest. The pulsating tumor was connected with the apex impulse, which was in the seventh interspace half an inch within the anterior axillary line. It was distinctly expansile. There was no thrill present nor any diastolic shock. It was rather forcible and lifted the palpating finger in all directions. The radials were palpable. The pulse was somewhat irregular in rhythm and much weaker than one would expect from the heaving character of the apex impulse. There was no perceptible irregularity of the pulses nor appreciable collapse. The lower border of the liver could be felt below the right costal border on deep inspiration. The spleen was barely palpable, and there was little tenderness in these regions.

Percussion: The note over the left lower chest posteriorly was very dull, almost flat. The area of cardiac dulness was markedly increased downward and to the left, where it did not extend beyond the limit of the apex impulse. Dulness extended also to the right of the sternum.

Abdominal Cavity.—There was a considerable quantity of free fluid.

Auscultation: Over the lungs the breath sounds were feeble and indistinct at both bases, especially posteriorly. The heart sounds at the apex were distinct and no murmurs were asso-

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ciated with them. At the base there was a soft, feeble murmur, heard only in the third interspace to the right of the sternum. This had very little, if any, area of transmission, and pressure with the stethoscope did not intensify it. Neither the aortic second nor the pulmonic second was accentuated. The urine and blood were not examined.

Diagnosis.—The diagnosis of fibroid myocarditis, hypertrophy and dilatation of the heart with cardiac insufficiency and aneurism of the left ventricle was made. Dr. Frank Jones saw the patient and concurred in the diagnosis.

The patient continued in the hospital, being up and down until February 8, when he expired suddenly on getting up to stool.

Autopsy.—Thirty-six hours after death; nutrition fair, weight about 150 pounds; height about 5 feet 10 inches; skin sallow. Scar 1 x 2 inches just above the right nipple. Globular enlargement over the fifth, sixth and seventh interspaces two and a half by three inches wide, two inches outside the nipple line. Abdomen distended; lower extremities edematous to the body. Rigor mortis not marked. No decomposition. Postmortem lividity in all dependent portions of the body and about the shoulders. Irregularity of the right pupil. Some of the mediastinal glands enlarged. Both pleuræ adherent. The left pleura markedly thickened; no fluid in either pleural cavity.

Pericardium: Adherent to both pleuræ. Both layers thickened. The parietal layer completely adherent to the epicardium, obliterating the pericardial cavity. The heart enormously enlarged and removed with the pericardium; removal effected with great difficulty, owing to the dense adhesions of all the structures in the mediastinum. Weight after opening with all clots removed, 1,145 grams (48.5 ounces). Blood in all the cavities. Chicken-fat clots in the auricles. The walls much hypertrophied and the cavities dilated; the left ventricle wall 1 inch, the right 5/16 inch thick. A large dilatation about the size of an orange sprang from the apex of the left ventricle anteriorly. The communication with the left ventricle marked by a well-defined fibrous ring 2 inches in diameter. The width of the swelling, at the greatest diameter, 5½ inches; depth, 3 inches. The sac formed by roughened endocardium and myocardium (which was thicker on the anterolateral surface, but only about one-fourth as thick as the ventricular wall, the posterolateral wall being apparently without myocardium, very thin), and both layers of the pericardium adherent at the apex to the pleura and a portion of the seventh

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rib, which was partially eroded. The cavity filled with dark clotted blood.

Pulmonary Orifice: Three and a half inches in circumference, valves thin, smooth and apparently competent. Tricuspid ⅞ inch; valves smooth and closing orifice.

Aortic Orifice: Two and three-fourth inches. Valves not sclerotic. Orifice apparently closed by valves. Slight fenestration of the middle cusp.

Mitral Orifice: Four and seven-tenth inches. Valves normal.

Heart Muscle: Fibroid changes.

Coronaries: Open in the auriculoventricular grooves. Orifices somewhat contracted. Vessels sclerotic.

Root of Aorta: A few recent atheromatous patches.

Kidneys: Enlarged; left larger than the right. Left peculiarly lobulated, containing an old scar and a small cyst. Capsules stripped with difficulty. Surface red; on cut surface, fibrous tissue increased. Cortex somewhat thickened. The organ dripped blood.

Abdomen: Peritoneum smooth except in the hepatic region, and contained a large amount of dark fluid.

Gall Bladder: Filled with a dark greenish fluid; walls thickened. Slight adhesions to surrounding structures.

Liver: Enlarged. Dark red. Surface uneven, hobnail in places. Fibrous tissue distinctly increased. The organ dripped blood. Capsule thickened, presenting the appearance of Curschmann Zuckergussleber.

Spleen: Enlarged. Cut surface dripped blood. Fibrous tissue increased. A supernumerary spleen about the size of an English walnut attached to the organ.

Microscopic Examination.—Sections of tissue were fixed in formalin, embedded in celloidin and stained with hematoxylin and eosin for microscopic study.

Heart: In some areas the terminal coronary arteries were blocked, showing typical anemic infarcts. The fibrous tissue was generally increased. In many areas the muscle cells were necrotic, which seemed to be the result of lack of nutrition. Endarteritis had caused obstruction of the arteries, which formed areas of fibrous myocarditis of, what Cowan describes as, the para-arterial type. There were also areas of fibrous overgrowth—perifascicular fibrosis—which corresponded to the same author's periarterial fibrosis.

Sections through the aneurism showed adhesive pericarditis, degeneration of the myocardium and marked overgrowth of fibrous tissue.

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Pathologic Diagnosis.—**Hypertrophy and dilatation of the heart, fibrous myocarditis, aneurism of the left ventricle, mediastinopericarditis, cirrhotic liver, multiple serositis, and cirrhotic kidney. The microscopic findings in the liver should have been included, as these are important in connection with mediastinopericarditis.**

CAUSES AND USUAL LOCATION OF ANEURISM OF THE HEART.

According to Warthin, aneurismal dilatation of the heart wall may be congenital, due to defective development of the heart muscle, and found in infants and young children. This may occur in any part of the heart wall, but is more frequent in the membranous portion of the ventricular septum.

The acquired form may be acute or chronic. The former may be due to inflammatory process in the heart. In this case the upper part of the septum is likely to be the seat, especially if the result of acute mural endocarditis; or a dissecting aneurism may result. Myomalacia cordis may be the starting point of this form of aneurism, which usually increases rapidly in size and progresses to rupture.

The majority of these dilatations, however, are chronic and result from the weakened cardiac wall giving way under intracardial pressure. This may occur at any age, but more frequently in advanced life. Walshe, writing on the subject in 1851, says that it has hitherto been most frequently observed between the ages of 20 and 30 and in very advanced life, or in those periods of life when the agents are operative in producing the cardiac changes on which the condition depends, namely, syphilis in the young and the various heritages of old age, senility and fibrosis.

For the same reason it is much more frequent in men than in women. In a total of two hundred and eight cases collected by Hare from various authors, he found that 74 per cent. were in males and 26 per cent. in females.

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Several pathologic processes have been described as giving rise to the weakening of the cardiac wall which results in aneurism.

According to Cowan, whose admirable work on the fibroses of the heart I have drawn on in the preparation of this paper, the French writers especially have suggested that pericarditis may be an occasional cause of aneurism. He describes the theory of these writers thus:

> If the two layers become adherent over a small area, the point of adhesion will be less mobile than the rest of the heart, and, with each systole, traction will be put on the part, and in course of time dilatation will result. The initial inflammation produces alterations in the superficial myocardium, and the chronic irritation resulting from the constant stress of the traction gradually leads to a fibrous condition of the aneurismal sac. . . . The objection to this theory may be stated as follows: Local pericardial adhesions are common and aneurism is rare, and the myocardium is but little involved in chronic pericarditis. I have never seen any fibrosis from such a cause even remotely resembling the fibrous sac of an aneurism. The pericardium, too, is not a fixed point, and it seems more reasonable to suppose that it and not the heart wall is dragged on by the systole of the ventricle. It is only in rare cases, where mediastinal adhesions fix the pericardial sac to the bony thorax, that such a mechanism seems possible.

I have quoted thus at length because the pathologic findings in my case apparently bear so directly on this point.

The widespread mediastinopericarditis, the firm union of the two layers of the pericardium over the aneurism, and their adhesion to the chest wall, would at first sight seem to furnish an ideal example in support of the theory of origin of aneurism from pericarditis. A more careful study of the case will, I think, show the widespread fibroid changes in the myocardium due to sclerosis and thrombosis of the terminal branches of the coronary arteries. The fact that the obliterated pericardial cavity is clearly recent over all areas except immediately over the aneurism, and the fact that mediastinitis is also more recent than the aneurism, show that pericarditis

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is at all events not the most important factor in the production of the aneurism.

Scars resulting from traumatism to the heart muscle and from gummata have also been shown to be rarely the cause of these aneurisms.

Most authors state that the conditions may occasionally depend on fatty degeneration independent of myocardial fibrosis. Cowan again thinks that the evidence here is not conclusive. There was no evidence of fatty degeneration present in my sections.

Undoubtedly the great bulk of the cases are due to myocardial fibrosis which results from the complete or partial obliteration of the coronary arteries—which, I think, is the cause in this case.

This explains also the most frequent seat of the lesion, which is in the apical third of the left ventricle, and most frequently here on the anterior surface.

According to Hall's statistics, the site of the aneurism in 112 cases was as follows: Left ventricle, 92 cases; right ventricle, 1 case; left auricle, 2 cases; ventricular septum (muscular part), 8 cases; ventricular septum (membranous part), 7 cases; auricular septum, 2 cases (Hare). This also coincides with the fact pointed out by Huchard that the left coronary artery, the descending branches more especially, is much more frequently abnormal than the right.

The aneurisms vary in size, from the size of an English walnut to the size of a child's head. They are usually single, but may be multiple. The opening into the cavity of the heart is usually large, but it may be small, rendering the aneurism distinctly saccular. The sac contains clotted blood, and the walls are composed of endocardium, myocardium and both layers of the pericardium, which is nearly always densely adherent. It may erode the chest wall, as this one had partially done.

SIGNS AND SYMPTOMS.

There are no distinctive symptoms of cardiac aneurism, although, as Walshe says, almost every known

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symptom of cardiac disease has been present in these cases. Physical signs are usually equally lacking. It is only when the aneurism is large and favorably located that an antemortem diagnosis is possible. It was the expansile tumor clearly connected with the apex and its heaving character associated with a very weak pulse which enabled us to arrive at a diagnosis in this case. How seldom the diagnosis is made may be seen from the statement of Hall, who says that an antemortem diagnosis was made only once in seventy-six cases.

The signs and symptoms present are almost always due to the associated pathologic conditions, chiefly to chronic myocarditis, which was prominent in this case. These symptoms may, however, be any one of those characteristic of the three clinical groups of myocardial diseases, namely, those in which sudden death may occur without previous indications of heart trouble, those in which there is arrhythmia, cardiac asthenia, etc., and those with general arteriosclerosis and hypertrophy and dilatation of the heart.

ASSOCIATED LESIONS.

This case illustrates so well those cases described by Pick as pericarditis, with pseudo-cirrhosis of the liver and known under a variety of names, such as mediastinopericarditis, multiple or polyserositis, Concato's disease, perivisceritis, etc., that I wish to speak concerning the diagnosis of this feature of this, to me, very interesting case.

These cases of mediastinopericarditis may be divided into three groups clinically: 1. The silent, without signs or symptoms. 2. Those presenting all the features of cardiac disease. 3. Those in which the main features are hepatic.

In this case, while the physical signs of adherent pericardium were not prominent, the evidence of thickened pleura, the fixation of the apex beat and the frequency with which concretic pericardii is known to occur with cardiac aneurism, together with the hyper-

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trophied and dilated heart, the enlarged and tender liver, and especially the marked ascites, out of proportion to the amount of edema present, should have led to the recognition of this condition which was found at autopsy.

TERMINATION.

In rare cases the sac has been obliterated by laminated clots. It is surprising how few of these chronic cases terminate in rupture of sac. Legg found this termination in only 7.7 per cent. of ninety cases. By far the most frequent termination is from cardiac insufficiency from myocarditis, as was the mode of death in this case.

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DISCUSSION.

DR. ROBERT PREBLE, Chicago, (exhibiting a boy with a cardiac aneurism): This patient was shot a few months ago, the bullet entering to the left side of the sternum and at the time giving no special cardiac disturbances. Later the patient developed a characteristic aneurism at the upper and outer portion of the left ventricle.

DR. JAMES B. HERRICK, Chicago: Dr McElroy's paper recalled the case, seen by me five or six years ago, of a colored man, about 30 years old. At autopsy, in addition to some valvular trouble, extensive adhesions and a mediastinopericarditis were found, as well as a chronic fibrous myocarditis. In one of the areas of cardiac softening, near the tip of the left ventricle, a rupture of the myocardium, evidently preceded by an aneurismal dilatation, had occurred; this rupture, instead of occurring directly into the open pericardium, occurred in a weakened spot between the two adherent surfaces of the pericardium that were apparently dissected apart by the blood. This little sac of pericardium had, at the time of death, reached the size of a goose's egg. The interesting clinical feature in this case was that, high up in the epigastrium beneath the xiphoid cartilage, was a visible, palpable, pulsating tumor, and over this could be heard a systolic bruit. The case presented many perplexing clinical features which made the diagnosis somewhat difficult. It was only at autopsy that the real nature of the trouble was learned; then the little sac communicating with the left ventricle was clearly disclosed.

DR. WILLIAM J. BUTLER, Chicago: I had a patient, a boy, 10 years of age, who had primarily a congenital stenosis of the pulmonary arterial tract. He acquired a septic endocarditis involving the pulmonary orifice. In addition to this, which

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had been diagnosed clinically, there was found at autopsy an aneurism, the size of a walnut, of the right ventricular wall. It had apparently resulted both from an involvement of the mural endocardium and underlying myocardium in the inflammatory changes, more or less fatty degeneration of the myocardium in general and the increased pressure in right ventricle.

Dr. James B. McElroy, Memphis: The diagnosis of these conditions is possible only when the aneurism is favorably located. A most favorable and valuable diagnostic point is the heaving character, the apex-impulse and expansile character, which is only possible when the aneurism is favorably located; then and only then, in my judgment, is a diagnosis possible. In contrast to ninety cases diagnosed postmortem, I have met but one case that was diagnosed antemortem.

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CLINICAL ASPECTS OF TUMORS OF THE MEDIASTINUM,

WITH CONSIDERATION OF THE FINDINGS IN FOUR CASES.*

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The records of hospitals and postmortem rooms show that mediastinal neoplasms, whether primary or secondary, are uncommon. Of more than 7,500 autopsies on patients dying from all causes at the Marine Hospital, Cronstadt, one in fifty exhibited mediastinal growths. It has been estimated that one medical patient in 10,000 shows mediastinal tumor of some form. Of more than 25,000 general hospital patients at the University of Michigan Hospital, there have been, perhaps, a dozen cases of tumor of the mediastinal structures. It is extremely interesting, therefore, that within the past year and one-half there have come under observation four cases in the Medical Clinic presenting strong presumptive evidence of mediastinal growth and, in addition, two in which the diagnosis was suspected. Perhaps this increased ratio is largely due to the increasing perfection of clinical aids in the examination of patients generally.

In order to make clear the consideration of our cases, perhaps a brief review of the anatomy of the region commonly known as the mediastinum will be pardoned. The mediastinum is that interval between the pleural

* From the Clinic of Internal Medicine of Prof. George Dock.

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sacs. It extends from the neck to the diaphragm. The vertebral column is behind and the sternum is in front. For convenience, the space is divided into a superior space, which includes that portion above a plane passing between the junction of the gladiolus and the manubrium and the fourth dorsal vertebra, and an inferior space comprising all below. The inferior space is again divided into anterior, middle and posterior spaces. A knowledge of the structures contained in each of these spaces is important, inasmuch as it furnishes a guide to the size, position and extent of suspected growths. This seems especially desirable in view of proposed operations. The superior space contains, in addition to muscles, the transverse portion of the arch of the aorta, the innominate, the left carotid and the subclavian arteries; the superior vena cava, the innominate and the left superior intercostal veins; the pneumogastric, cardiac, phrenic and the left intercurrent laryngeal nerves; the thoracic duct, the remains of the thymus, the trachea and esophagus and numerous lymphatics. The anterior portion of the inferior space lies between the edges of the pleura and in it are the internal mammary vessels of the left side, a few lymphatic glands and a quantity of loose areolar tissue. The middle portion of the inferior space is largely occupied by the heart in the pericardial sac. In addition there are also the great cardiac vessels, the bifurcation of the trachea, the structures at the roots of the lungs and numerous lymph glands. The posterior space is occupied by the lower part of the aortic arch, the thoracic aorta, the azygos veins, the thoracic duct, the esophagus, the pneumogastric and splanchic nerves and a few lymphatics.

It is readily seen that the symptom-complex presented by any class of mediastinal growths is largely dependent on the size and position of such growths. The great majority of tumors in this region arise in the anterior space of the inferior division. They are most commonly carcinomata, sarcomata or lymphomata and

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have their origin in thymus remnants, lymph glands and connective tissue. In the middle space the primary focus is generally the lymph tissue. The tumors in this region may be of almost any variety. In the posterior space primary tumors are relatively uncommon. They may arise from lymph tissue, from the lung or its adnexa or from the esophagus.

In general, the manifestations of the mediastinal growth depend on:

1. The nature of the neoplasm; it may be a well-localized, discrete mass; or it may by continuous spread involve the lungs, pleura, the air passages, the great vessels, the esophagus or the nerves; or it may be of such nature as to form metastases.

2. The size of the tumor: small masses may cause local symptoms on the part of adjacent structures; large masses by extending through all the mediastinal spaces may furnish a puzzling symptom-complex.

3. The general position: tumors of the anterior space may become early evident externally; those in the middle portion may be small but cause marked symptoms; those in the posterior division may early involve the gullet or thoracic duct.

Mediastinal neoplasms produce signs and symptoms mainly as the result of the pressure they exert on bony framework, blood vessels, nerves or air-containing tissue. One may expect thoracic deformity with protrusion of the sternum or caries of the spine. Pressure effects on the lung and its adnexa mean early dyspnea, with more or less cyanosis, cough with sputum that may be characteristic (as in the case of dermoids) or early effusion into the pleural sacs, causing interference with diagnosis. Pressure on the heart or the great vessels results in embarrassed circulation in its widest sense. Pressure on nerves may cause cough, hoarseness or even aphonia, alterations in the size of the pupils, changes in the heart rate or rhythm or reflex disturbances in the abdomen. Involvement of the gullet pro-

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duces dysphagia with starvation emaciation. Interference with the thoracic duct may bring effusions into the serous sacs. Depending on the malignancy of the process, there may be loss of weight, weakness, anemia and metastatic foci.

The four cases furnishing the material for this communication are interesting from many standpoints. One of them, a case of chronic cyanosis with erythremia, is unique. The diagnosis in all instances was presumptive, so far as absence of postmortem material is concerned, but sufficient evidence is at hand to make the conditions reasonably certain. All the patients were adults. There were three males and one female. The youngest patient was 43, the oldest 67. They came to the hospital for such ailments as heart disease, asthma, chronic bronchitis, Bright's disease and laryngeal obstruction. Three of the patients appeared to have affections primary in the thorax. In the female the process was evidently secondary. Two patients had rapidly-spreading, malignant growths, and death supervened within less than a year after they came under observation. In the remaining cases the neoplasmata are apparently of slow growth and the patients have been affected for some years.

REPORTS OF CASES.

CASE 1.—This presents the clinical picture of chronic cyanosis, with variable erythremia, but without evident splenic enlargement; attacks of asthmatic dyspnea; albuminuria; involvement of the mediastinal tissue as shown by symptomatic, physical and radiographic examination.

Patient.—There was sent to the medical clinic in January, 1907, an American laborer, aged 43, with complaints of difficulty in breathing, palpitation, frontal and occipital headaches, chronic cyanosis, dropsy and general weakness.

History.—The family history of the patient was negative, with the exception that his mother recently had an amputation for a thyroid tumor in the right tibia. Up to the age of 30 the patient was in good health. At this time he began to have asthmatic attacks, coming on at irregular intervals,

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usually at night. The patient's habits were good, and there was no history of specific disease. About six years before entering the hospital, he had what he termed a severe attack of "asthma," at which time his "wind was shut off sudden" by a "pressure just at the top of the breast-bone," and he became unconscious. He remained so for a few minutes. He had palpitation of the heart for some time afterward. About four years since he noticed blueness of his face, hands and feet, with variable swelling. He took medicine and believed that the blueness almost disappeared. It did not again become marked until September, 1906. At this time palpitation and cardiac distress, together with blueness, were so marked that he consulted a physician, who informed him that he had heart disease. He was put on treatment, but relief was only temporary. His blueness increased, becoming especially marked when he worked or when he was excited; palpitation and dyspnea became more troublesome. He began to have severe frontal headaches, was frequently dizzy and his eyes became prominent. A feeling of thoracic constriction was almost constant, particularly when he lay down. This feeling was most apparent in the region of the nipples. A blow on the chest or pressure downward from above the sternum produced a sensation of "smothering." There was no difficulty in swallowing, and no marked gastrointestinal disturbance.

Examination.—This revealed a man of medium build, with thin panniculus. There were no pronounced evidences of emaciation. Over the face and neck, particularly the nose, chin, lips and ears, there was a startling degree of cyanosis. The hands and feet were moderately blue, particularly so when the patient stood or allowed his arms to hang down. Then the cyanosis came on almost instantly and the peripheral veins were markedly prominent. When the patient lay down the face and neck were slaty blue. The cyanosis was less marked after he had lain for a few minutes. Exercise and psychic disturbances deepened the color perceptibly. The palate and tongue were deep purple. The eyes were very prominent, especially the right eye, that eyeball protruding 6 mm. further forward than the left. The conjunctivæ were suffused, the right more than the left. The pupils were of moderate size, equal and active. The external jugular veins were injected and prominent. They filled from above. There was moderate pulsation of both carotids, rather more on the right. The thyroid was negative. There was no tracheal tug. Over the trunk the skin had a bluish cast. There was a fine punctate eruption over the chest (medication?). The thorax moved *en cuirasse*. The inspirations were shallow and not ac-

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companied by much abdominal movement. There were no visible Litten's shadows, but there was slight inspiratory retraction in the lower axillary spaces. The respiration rate was not increased when the patient lay quiet. It was rapidly increased on even slight exertion. The heart beat was faintly visible in the fifth interspace, well inside the nipple. It was not increased in rate. Palpation of the lungs was negative.

Percussion is indicated in Figure 1. The liver dulness was low, the spleen barely made out. There was an abnormal substernal dulness, with an atypically situated precordial outline. The areas of dulness did not change with change in position of the patient. Outside the areas of actual dulness there was a poorly defined zone of diminished resonance. Traube's space was tympanitic in a small area in front. The liver dulness began at the tenth rib in the mid-scapular line, posteriorly.

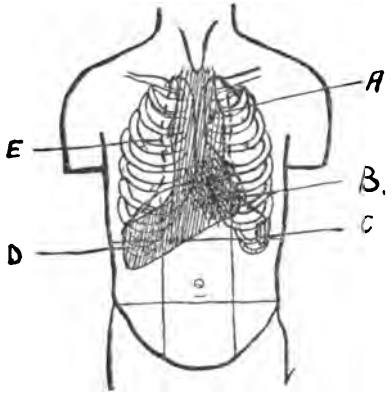

Fig. 1.—A, atypical thoracic dulness; B, cardiac dulness; C, spleen; D, liver; E, area of diminished resonance.

Auscultation of lungs: There was diminished vesicular breathing throughout the entire right side to the fifth rib. Below, the inspirations were sharp and blowing, the expirations soft and prolonged. Over wide areas there were few piping râles. On the left there was bronchovesicular breathing to the second rib, with increased vesicular breathing below. The râles were more numerous and more pronounced on the left than the right. The voice, both spoken and whispered, was negative The examination of the back added nothing to the picture.

Auscultation of the heart: All sounds were heard with difficulty. The first sound at the apex was heard best two fingers' breadths inside the mid-clavicular line in the sixth

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intercostal space. The sounds over the base were best heard in the fourth left space and beneath the adjacent sternum. The first sound at the apex was soft and somewhat impure; the pulmonic second sound was moderately accentuated. The radial pulse was slow, of moderate size, and fuller on the left than on the right. There was moderate sclerosis of the radials. The blood pressure varied with the side tested. On the left, the pressure was, systolic 156 mm. Hg, and the diastolic 109 mm. On the right the systolic pressure 146, the diastolic 98, with the Erlanger apparatus 12 cm. cuff.

Abdomen was somewhat distended in the region of the navel. The liver was felt with difficulty at the end of inspiration. The spleen was not palpable in whatever position the patient lay. There was no palpable mass in the abdomen. The glands were negative.

Eyes: There was moderate conjunctival injection; the retina and head of nerve were edematous; there was marked venous engorgement; no hemorrhages (Professor Parker).

Nose: There was partial occlusion of the left nasal fossa.

The larynx was negative.

Blood examination: Erythremia was noted from the first. At entry, as seen in Chart 1, the red-cell count was 6,450,000. The hemoglobin was 100 per cent. plus. The white cells were about 6,500. The blood was very deep red, flowed slowly and was extremely viscous. It was spread on a slide with great difficulty. There was nothing peculiar about the shape or the size of the red cells. No nucleated reds were seen. The differential white count was as follows: Small lymphocytes, 14.8 per cent.; large lymphocytes, 3.8 per cent.; polynuclears, 67.6 per cent.; eosinophile polynuclears, 3.8 per cent.; mast cells, 1.6 per cent., and degenerates, 8.4 per cent. Further consideration of the blood appears below.

Urine: This contained a moderate amount of albumin, with many small, finely and coarsely granular casts and numerous cylindroids.

Fluoroscopic examination: A diffuse, non-pulsating shadow lay above the heart. It was especially dense about the root of the lung and the great vessels. It could be followed up into the neck. The heart was downward and inward. The diaphragm was low down on both sides, especially on the right.

Radiogram: The fluoroscopic findings were confirmed. The mass evidently filled the mediastinum and was almost as dense as the heart. No definite lines of pulsation could be seen. The tumor appeared to occupy both mediastinal spaces, lying in close approximation to the heart, lungs and their

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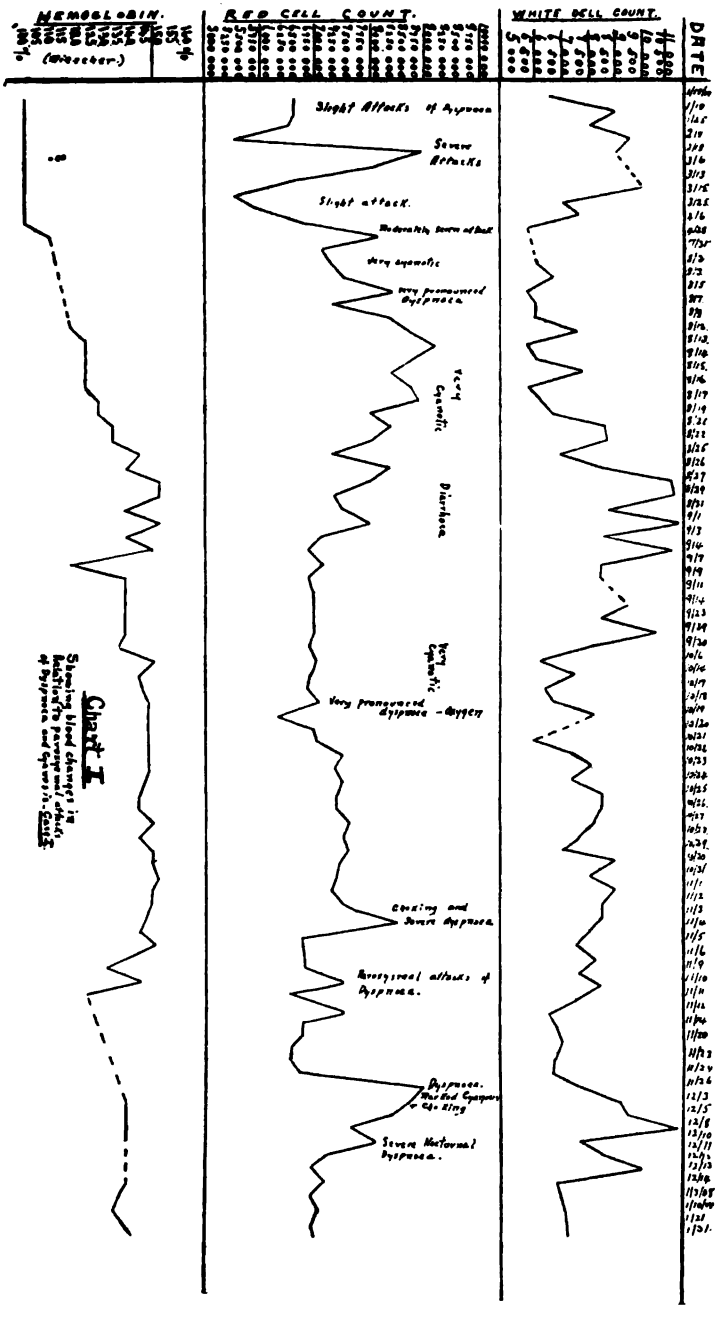

Chart I.

Showing blood changes in Rodriguez pernicious anaemia of Dyspnoea and cyanosis. Case I.

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adnexa. Here and there points of greater or less opacity might be seen in the lungs and pleura. There appeared to be more infiltration to the left than the right.

Subsequent History.—The patient was kept quiet for a few days, and in view of the high blood pressure and cyanosis, put on purges and nitroglycerin. He improved and was soon up and about. His remaining history to date is particularly interesting. It may be roughly divided into two periods. The first was a stage of moderate cyanosis, with erythremia, in which the patient was generally comfortable and able to do light work. There were days when the cyanosis was rather marked, and when feelings of fulness, with difficult breathing, were complained of. This was especially the case when the patient worked hard or became excited. There was little nocturnal dyspnea. The blood pressure was generally lower than at entry, either because of the rest or potassium iodid, or both. It gradually fell to an average of systolic 96 and diastolic 75 mm. Hg.

The second phase of the history comprised periods of extreme cyanosis with more or less pronounced erythremia; marked dyspnea, bearing usually some relation to exertion or excitement, associated with unconsciousness, stupor or apathy; disturbances in vision; paroxysmal headaches; albuminuria and gastrointestinal symptoms.

Marked Clinical Manifestations.—1. Cyanosis. As stated, the patient was always cyanotic. There have been, however, since he came under observation, seventeen "attacks" of extremely pronounced cyanosis, general in character, but especially involving the head, neck, upper part of the thorax, and the extremities. At these times the color of the face and the extremities was a dusky, slaty purple, while over the trunk the skin had a bluish cast. On several occasions there was slight nose bleed. There was never bleeding from the mucous surfaces. Hematuria was not observed. With the occurrence of the cyanosis, the patient suffered extreme dyspnea. The respirations were greatly accelerated and the inspirations audible and slightly crowing. The expirations were prolonged, and sometimes accompanied by an expiratory grunt. In these attacks the voice was hoarse, or merely a low-pitched whisper. Sensations of pressure in the substernal region, with feeling of suffocation, palpitation with or without precordial distress were complained of. The dyspnea sometimes lasted for but a few minutes, then again persisted for half an hour or as long as the greater part of a day. The attacks were frequently followed by days of added cyanosis and prostration. During the attacks the heart rate was

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accelerated, going as high as 130 when it had previously been in the neighborhood of 60. There were never evidences of actual cardiac incompetency. The peripheral vessels were greatly injected, but positive venous pulsations were not observed. Auscultation of the lungs in the acute attack revealed an almost entire absence of breath sounds, with few high-pitched musical râles. The eye-grounds generally showed extreme engorgement of the retinal vessels with marked edema of the fundus. The right eye was sometimes very prominent, and there was a noticeable increase in intraocular tension. The conjunctivæ were markedly suffused, particularly the right one.

2. Erythremia: Coincident with the attacks of added cyanosis and dyspnea, there were generally noted changes in the red-cell count and the hemoglobin. The white-cell count was sometimes altered, in proportion. These blood changes were usually in proportion to the severity of the "attacks," but not always so. As will be seen from Chart 1, there were periods of intense cyanosis with red-cell count not greater than 6,500,000. On several occasions there were days of pronounced cyanosis, without acute dyspnea, when the red-cell counts ranged from 7,000,000 per c. mm. to as high as 9,000,000. Differences in count were noted, varying with the part of the body from which the blood was taken. For example, the blood taken from the toe in one attack gave red cells 7,780,000; that from finger, 7,200,000; while that from the ear was 8,020,000 cells per c.mm. The hemoglobin was not estimated at this occasion. On another test, when the cyanosis was not very marked, the finger gave 6,260,000 red cells per c.mm. with hemoglobin 1.36 per cent. (Miescher); that from the toe 6,860,000, with hemoglobin 156 per cent., while the blood from the ear was 7,010,000, with hemoglobin 144 per cent. It will be seen that the hemoglobin appeared to vary with the vascular distance from the heart, rather than with the actual increase in the red-cell count. The highest blood counts were recorded during the attacks of most acute dyspnea and cyanosis. There were six occasions on which the red-cell count ranged from 7,250,000 per c. mm. to as high as 9,260,000 per c. mm. On one occasion there was a period of ten days when the count was above 8,000,000 per c.mm. The white-cell count was not always proportionately increased. (Chart 1.) The counts were never much higher than 10,000. The hemoglobin estimations could not be made with the ordinary Tallquist scale. With the Miescher apparatus, and with dilution to twice the usual extent, the estimations always ran considerably above 100 per

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cent. (Chart 1.) The variations were from 105 per cent. to 156 per cent. The relation of the increases to the erythremia and the attacks of cyanosis and dyspnea is well shown in the chart. During the period of prolonged cyanosis already mentioned with counts above 8,000,000 per c.mm., the average hemoglobin reading was 132 per cent. (Miescher).

The differential white-cell counts showed very little variation from that already cited. More recently, there was a slight increase in the eosinophiles, and small lymphocytes, with the appearance of a rather large proportion of myelocytes following one of the acute attacks. Nucleated red cells were noted. During none of the attacks was the spleen palpated. Recently, an estimation of the specific gravity of the blood by Hammerschlag's method was 1.062, when the red-cell count was 7,400,000. The coagulation time was difficult to estimate with the pipette method, because of the extreme viscosity of the blood. By the slide method, coagulation was frequently complete at the end of a minute in an ordinarily warm room. It was often less than this. Unfortunately, no estimations of relations between corpuscles and plasma nor the amount of alveolar carbon dioxid are at hand.

3. Unconsciousness: In one of the attacks unconsciousness lasted for several minutes. There was partial consciousness with urgent dyspnea for nearly half an hour following, and the patient was apathetic for several hours.

4. Disturbances in vision: These were frequent. At times there were merely spots before the eyes with blurring of images. On one occasion, there was diplopia. During the most severe attack of dyspnea, "everything turned black" before unconsciousness supervened. The pupil on the right was generally dilated during the dyspneic periods. Strabismus was not noted. The eyeballs were both prominent, particularly the right.

5. Albuminuria: This was present at the time that the patient came under observation. At first it appeared to be aggravated by the attacks. It was not, however, always present at or following the attacks. The amount has recently increased greatly. There has been as large a quantity as one-third volume. Casts, mainly of the granular variety, have been almost constant. Generally, there has been an increase following the acute dyspnea and erythremia. The attacks do not appear to have much effect on the blood pressure. Under rest and medication (?) the pressure has fallen from an average above 150 mm. Hg. systolic and 100 mm. Hg. diastolic at entry, to average systolic of 108 mm. Hg. and diastolic between 75 mm. Hg. and and 80 mm. Hg., with the Erlanger apparatus.

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In one of the very severe dyspneic periods, the systolic pressure was 100 mm. Hg. and the diastolic 60 mm. Hb. At this time the heart action was very weak.

6. Paroxysmal headaches: These usually bore some relations to the dyspnea and the added cyanosis. They frequently manifested themselves for some days previous to the actual attack, and often persisted for several days after the patient was otherwise comfortable. They were generally accompanied by visual disturbances.

7. Gastrointestinal disturbances: These were of more recent onset. Loss of appetite was early noted. There has never been dysphagia or vomiting. Test meals have not been deemed advisable. Paroxysmal pains beginning in the epigastrium and radiating to the lower abdomen were noted about ten months ago. The pain was extremely prostrating, and came on at one of the most severe attacks of dyspnea. The abdominal wall was rigid and the patient was bent double at each sharp stabbing pain. The bowels were constipated. Recently, there have been attacks of diarrhea. This was pronounced for about two weeks on one occasion and was associated with moderately high blood count. There was no elevation of temperature, and nothing characteristic about the stools.

Growth of the tumor: The more recent radiograms appear to show that the mass is gradually extending and that, in keeping with the added physical signs, is involving the greater part of both mediastinal spaces.

Summary.—The case presents many of the findings of the condition of chronic cyanosis with erythremia described by Vaquez, Osler, Cabot and others. The spleen is not, however, enlarged and there appears to be a discoverable cause for many of the symptoms noted, namely, the mediastinal growth. This is unusual or not yet reported at all in cases of true cyanotic polycythemia (Vaquez-Osler's malady). It is not quite determined that the two conditions do not exist, but in view of the rather marked variations in the cyanosis and the red cell count, it is probably that much of the erythremia is due to extensive pressure in the thorax on the great vessels. The changes in spleen and bone marrow may come on later and the patient take on more characteristically the classic picture of the erythremia vera.

Case 2.—*Patient.*—A German, boilermaker by trade, aged 43, entered the clinic on account of sense of constriction across the chest, with occasional choking sensation in the throat; insomnia; constant morning nausea without vomiting; shortness of breath with gasping inspirations, weakness, dizziness and headaches.

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History.—This negative except for chronic alcoholism and the use of much tobacco. About a year ago he began to note that after eating he had a heavy sensation in the upper epigastrium and that his head felt full. He was unable to sleep at nights on account of a sense of pressure beneath the sternum. He was constantly nauseated in the mornings, but never vomited, although he tried hard enough. He began to get "winded" with little exertion and people noted that his face was becoming abnormally red. His voice became rather husky, and his breathing was often difficult with "a whooping when he drew in his breath." He became so uncomfortable that he had to give up work. His feet were sometimes swollen; he had headaches and often noticed spots floating before his eyes.

Examination.—This revealed a thick-set, florid-faced man with anxious expression. The respiration rate was 30, and the patient was unable to lie comfortably even when propped up by three pillows. Occasionally there was prolonged, crowing inspiration. There was frequently a short superficial cough without sputum. The skin of the forehead, face, ears, neck and upper part of the thorax, back and front, as well as the feet and hands was rosy red, with purple cast. The cyanosis was slightly increased in the dependent portions and on exertion. There was no peripheral edema. The eyes were prominent and the conjunctiva slightly injected. The tongue was bright red. The supraclavicular fossæ were full and retracted moderately during inspiration. There was no tracheal tug and no enlargement of the cervical glands. The chest was of the pronounced "barrel" type. It moved *en cuirasse* with slight lateral expansion. Litten's shadow was not seen on either side. There was retraction in the lower axillary interspaces during inspiration, especially at the time of the crowing inspirations. In the region of the nipple, the right thorax was rather fuller than the left. Tactile fremitus was increased below both clavicles. The percussion outlines were as in Figure 2. It will be seen that there was distinct atypical thoracic dulness in the mediastinal region. Apart from the dulness, the percussion revealed nothing beyond rather high degree of resonance over the lung. Traube's space was tympanitic. The breath sounds were increased on both sides, especially on the left as far down as the fourth rib. The voice sounds were increased in the left upper and in the back, below the tip of the scapula. The heart was not displaced, but appeared enlarged to the left. The sounds at the apex were rather short and sharp. There was moderate accentuation of the pulmonic second sound. The radial pulse was small, rather quick, regular. The right radial seemed somewhat

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fuller than the left. The blood pressure read with Erlanger, 12 cm. cuff: systolic, 188 mm. Hg; diastolic, 140 mm. Hg. The abdomen was distended, full in the flanks. The liver descended just below the edge of the ribs in the nipple line at the end of deep inspiration. There was no ascites. The superficial glands were negative.

Otolaryngological examination: Both cords abducted to the cadaveric position and were slightly retracted. They showed moderate injection. On phonation, the right cord was negative; the left showed imperfect approximation to the vocal process posteriorly (Dr. M. L. Cushman).

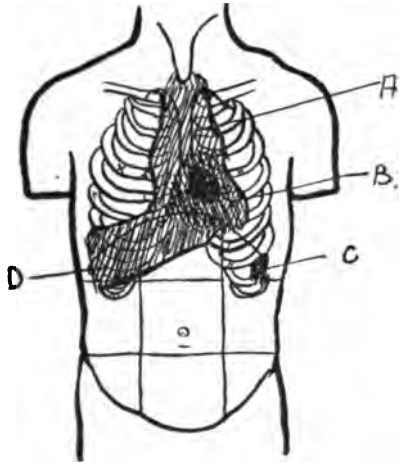

Fig. 2.—A, atypical thoracic dulness; B, cardiac dulness; C, spleen; D, liver.

Eyes: The retina was markedly edematous. The perivascular lymph sheaths of all the veins were prominent; there was disseminated chorioiditis in and about the macular region. Vision O. D. 15/30; O. S. 15/200. (Dr. G. Slocum.)

Reflexes: These were negative; there was marked tenderness along the posterior tibial nerve.

Blood: The red-cell count was 4,750,000; the white-cell count, 5,200; the hemoglobin, 100 per cent. (Tallquist).

Urine: This was negative.

Stomach: There was mucous gastritis with diminished acidity, but good motility.

Fluoroscope: The heart appeared hypertrophied. Occupying the mediastinum was a mass of about the same degree of opacity as the heart. It was continuous with the heart outline, and extended upward to the neck. In its upper part, it

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extended more to the left than to the right. Low down it filled in the cardiohepatic angle.

Radiogram: This confirmed the fluoroscopic findings. The mass was especially thick about the great vessels and the root of the lung. There were no evidences of pulsation.

Subsequent History.—The patient was put on purges and potassium iodid. He has shown improvement in blood pressure, which has dropped as low as 160 systolic, and in his subjective symptoms. The crowing breathing, the nocturnal dyspnea, and the morning nausea have become less marked. He is still cyanotic and complains of the sensation of tightness in his chest. It is aggravated by excitement or hard work. The tumor appears to be enlarging into the posterior mediastinum and to the left. A distinct area of dulness may be percussed in the left back along the spine from the level of the inner end of the scapular spine to the eighth dorsal vertebra. In this region there is marked increase in the vocal resonance and suggestion of tubular breathing. The crowing inspiration is still marked, but not so evident as when the case first came under observation. There is no dysphagia, and no obstruction or pain when the stomach tube is passed. The patient says that he has coughed up or vomited up some "stuff" streaked with blood, but we have never been able to get any of it for examination in the clinic.

CASE 3.—*Patient.*—A woman, aged 64, likewise showed chronic cyanosis as a pronounced clinical manifestation. At first, there was some polycythemia, the red-cell count reaching 6,640,000, but this was transitory.

History.—The patient had had a carcinoma of the left breast removed three years before entering the hospital. She came to us on account of pain in the left side of the chest, swelling of the neck, with "rushing of blood" to the head; weakness, nervousness and edema of the extremities. She presented a negative family and personal history with the exception of a peculiar, eczematous skin affection in early adult life. The breast tumor was noted fifteen years ago. She had it removed by a popular "cancer-plaster cure." It recurred with increased rapidity of growth, and three years since she had a radical operation on the breast and the left cervical glands. Shortly after the operation, the patient noted burning sensations in the wrists and the hands. Six months ago, she observed that the veins of the upper part of her chest and her left arm were growing more prominent; there were also soreness and a sensation of fulness in the upper part of the thorax in the median line. The head began to feel full and the neck to enlarge. She thought that it was now two

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inches larger than it had been six months ago. The left arm began to swell slightly. She had lost twelve pounds in weight in two years.

Examination.—The patient was a rather heavy-set woman, nervously inclined. She was very restless and loquacious. Her face and neck were scarlet, with a bluish tinge over the ears and the lips. Over the upper thorax and the left arm the superficial veins were prominent and enlarged. The superficial venules were dilated so that the entire region has a distinctly bluish cast. Both forearms were puffy-looking, especially the left, where there was slight pitting on pressure. The left forearm was also cyanotic, especially when dependent. The glands in the left axilla and the lower cervical group on

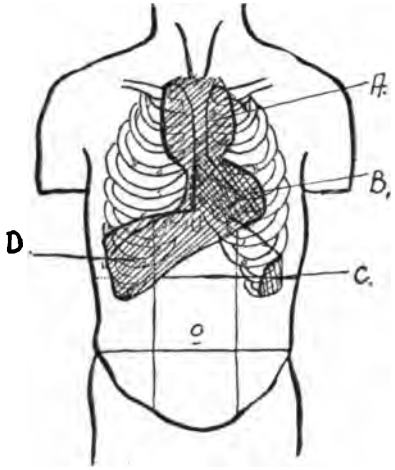

Fig. 3.—A, atypical thoracic dulness; B, cardiac dulness; C, spleen; D, liver.

both sides, particularly on the left, were enlarged. The eyes were moist, the lids swollen, the palpebral apperture small. The pupils were negative. The voice was rather hoarse. There was no tracheal tug.

Thorax: This was short and broad. The bony prominences were hidden by fat. There was no Litten's shadow on the right; it was fairly well seen on the left. There was slight increase in tactile fremitus below the right clavicle. The left infraclavicular space filled better than did the right. The percussion (Fig. 3.) revealed an easily made-out mass occupying the upper sternal region, and extending rather more to the right than the left. The remainder of the thorax was negative to percussion. On auscultation the breathing was dimin-

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ished on the left to the second rib and increased over a corresponding area to the right. Below it became quiet on both sides. Over both infraclavicular spaces the spoken voice had a distinctly nasal twang, which was more marked on the right.

Heart: This was negative, except weakness and the rather startling increase in the pulmonic second sound, without diastolic shock. The radial pulse was moderately full on both sides, the systolic pressure being 130 mm. Hg. (Erlanger, 12 cm. cuff.) There was no capillary pulsation.

Abdomen: The liver and the spleen were barely felt. The inguinal glands were negative. A mass or indefinite shape was made out in the lower left iliac region (secondary?).

Fluoroscope: A mass of rather globular shape filled the superior and anterior mediastinal regions. It could not be said to pulsate.

Radiogram: This confirmed the fluoroscopic findings. The mass was distinctly more to the right than the left. It was in close connection with the great vessels and the root of the lung. The heart appeared somewhat enlarged.

Subsequent History.—On account of the heart weakness, the patient was put on digitalis. She became rather more comfortable, but her subjective and objective symptoms and signs did not improve. She was at length lost sight of, but recently word reached us of her death. The autopsy was not secured.

Case 4.—This presented evidences of primary, malignant mediastinal tumor, in contrast to the secondary malignant tumor of Case 3. The disease appeared to run a rapid course, as the death of the patient has already been reported.

Patient.—He was brought to the hospital for "heart trouble." The man had been ill for about a year. The disturbance followed a severe attack of diarrhea, from which he never appeared to recover. His main complaints were loss of weight and strength, hacking cough with abundant frothy or watery sputum, shortness of breath and palpitation.

Examination.—The patient was tall, spare, emaciated, There was a trace of cyanosis over his lips and his finger tips. The face was dusky pale, with enlarged venules over the cheeks and the nose. There was an old conjunctivitis with eversion of the lower lid. The thorax was long and deep. The lower interspaces retracted on the left in the sixth and seventh axillary spaces, and slightly in the sixth on the right. The heart impulse was diffusely seen below the left nipple. There was poor thoracic movement on the right side, generally fuller than the left. The vocal fremitus was absent on the right below the third rib. The percussion is indicated in Figure 4.

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There was abnormal substernal dulness extending upward below both clavicles more on the right than the left. The heart was displaced or enlarged to the left. Absolute dulness began at the third space on the right and was movable. There was moderate Grocco's sign in the left back. Auscultation revealed quiet breathing on the right below the clavicle, and absent breathing below the third space. There was rather marked nasal bronchophony, without egophony. On the left both breath and voice sounds were exaggerated. The heart sounds were weak and impure.

Fluoroscope: After tapping, the heart was to the left. On the right there was diffuse opacity low down. The left diaphragm moved freely. There was no movement on the right.

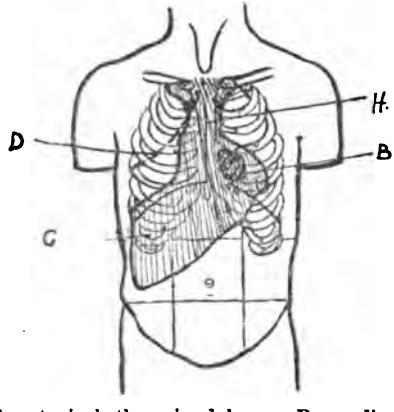

Fig. 4.—A, atypical thoracic dulness; B, cardiac dulness; C, liver; D, upper limit of pleuritic effusion.

Blood examination: Red blood cells 5,680,000; white cells, 7,550; hemoglobin, 85 per cent. (Tallquist). The blood pressure at time of entering was, systolic, 210; diastolic, 160 mm. Hg. The radials were very sclerotic.

The urine was negative.

The patient was tapped in the right pleural sac and 1500 c.c. fluid removed. The fluid contained numerous large, atypically built alveolar cells, with several nuclei and division figures, rendering a diagnosis of carcinoma highly probable.

Subsequent History.—The patient grew gradually worse. The fluid accumulated rapidly. He was again tapped and again the fluid returned. His cardiac weakness and his cough returned with increasing vigor after the tappings, and he barely reached his home before he died.

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SUMMARY.

Diagnosis.—It will be seen that the four cases detailed present a varied range of symptomatology. There were certain constant features. In each of the cases there was more or less marked cyanosis, dyspnea and cough. The physical examination, carefully made, with the patients stripped, revealed in each instance atypical, thoracic dulness. In Case 1 the heart was displaced by the growth; in Case 4 the cardiac displacement was due largely to the accumulation of fluid in the right pleural sac. In all the cases mediastinal infiltration was clearly shown by both fluoroscope and radiogram. In Case 4 the opacity was masked by the effusion, but became evident after tapping. The pressure signs are exceptionally interesting. In the first three cases cited the cyanosis and flushing were marked. Frequently there were in all cases paroxysmal exacerbations, brought on usually by exertion or psychic disturbances. In Case 1 these paroxysmal manifestations were striking. Distention of the veins of the neck and the arms was evident in Cases 1 and 3, especially in the latter. In Case 3 the distention of the veins was largely in the left arm and was associated with almost constant edema. There was also at times a brawny desquamation of the skin of the left arm and chest. In the first three cases there was more or less constant involvement of the vocal cords. In Case 1 this resulted occasionally in aphonia. In Case 2 permanent, partial paralysis of the left cord was noted. In all the cases there was pressure, more or less constant, on the pneumogastric, with tachycardia, precordial distress or abdominal pain as a consequence. Pressure on the bronchi was especially evident in Cases 1 and 2. The variation in the degree of pressure should be noted. In all the cases except that last described the evidences of constant, long-continued pressure were to be seen in the eye-grounds. This was particularly so in Cases 1 and 2. In these patients the eyes were also

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prominent, but not equally so. The right eyeball protruded rather noticeably in Case 1. The evidences of stagnation in the veins of the fundus was generally proportionate to the prominence of the eyes. In but one of the patients (Case 1) was peripheral edema at all constant. In all of the cases it was small in amount. Case 1 showed an increasing amount as the albumin in his urine increased. The subjective evidences of intrathoracic pressure are interesting and important. Sensations of "smothering," "fulness beneath the breast bone" and a "weight in the chest" were complained of. The cerebral congestion was associated with feelings of fulness in the head (frequently mistaken for fever by the patient), headaches, dizziness and disturbances in vision. Cough was present in all the cases. There was a suggestion of "brassiness" in Case 2, in which patient laryngoscopic examination revealed partial paralysis of the vocal cords. Tracheal tug was not observed in any case. No evidence of pulsation could be made out in the tumor area in any of the four patients. With the exception of myocardial weakness (Cases 3 and 4) the hearts were negative, so far as could be determined. Diastolic shock was not to be made out in any instance.

Without postmortem material the nature of the tumor masses in these cases can only be surmised. There is abundant proof that in Cases 3 and 4 the growths were carcinomatous. In Case 1 the process seems to be either a slowly growing sarcoma or a luetic involvement of the mediastinal tissues. No evidences of syphilis are discoverable, however. Case 2 is perhaps more clearly luetic than Case 1. There is no distinct history of syphilis, but the patient has reacted fairly well to specific medication.

A few words might be said as to the probable position of the growths. In Case 1 the symptomatology and the radiograms point to a rather general involvement of the entire mediastinum. The second case presents more evidences of involvement of the middle space of the in-

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ferior mediastinum than of a general involvement. In Case 3 the anterior and superior spaces were doubtless the seats of the greater degree of infiltration. In the last case the inferior space appeared to be the seat of the larger portion of the growth, with secondary involvement of the right pleura. The so-called "cancer cells" in the pleuritic effusion were a valuable diagnostic aid as to the primary cause of the fluid.

Treatment.—When the nature of the growth is evidently malignant, as in Cases 3 and 4, only palliative measures are indicated. These are governed by the symptoms. Care should be exercised in the tappings, when effusion exists. Too rapid evacuation of fluid, or the withdrawal of too much of it, may be followed by severe and exhausting cough, albuminous expectoration and collapse. Small, localized tumor masses may in picked cases be treated with *x*-rays with benefit. None of our patients appeared to improve under the exposures. The treatment should be given only by skilled operators, inasmuch as the long-continued exposures, which are evidently necessary, may give rise to severe burns and serious blood and kidney alterations. In our series Patients 1 and 2 appeared to improve somewhat under anti-syphilitic medication. If there is even a possibility of lues iodids may be tried in full doses. The high blood pressures are relieved by bleeding or, where this is impossible, by nitroglycerin or the nitrites. Daily purging is also of service, although this should be done with care, as frequently patients become exhausted from the free evacuations. The periods of extreme dyspnea (as in Case 1) are relieved by morphin and atropin hypodermically and the administration of oxygen. In a few instances it seemed that the oxygen exerted a favorable effect on the erythremia. When the dyspnea is continued through several days, absolute rest, with tincture of belladonna internally, make the patient more comfortable.

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Operative interference might be advised in cases in which the tumor mass is well localized, in which proper arrangements can be made for maintaining intrathoracic pressure and where an operator of the highest skill is at hand. Doubtless, with the improvement in diagnostic methods and more extended operative procedures on the thorax, surgical measures will become more general. The situation of the mediastinal tissues will, however, place certain barriers in the way of promiscuous attempts at enucleation or dissection of mediastinal neoplasmata.

In conclusion I wish to express my thanks to Drs. M. L. Cushman, George Slocum and Sobei Ide for aid in collecting data herewith presented, and to Dr. B. D. Niles of Grand Ledge, Mich., and Dr. G. A. Seaboldt of Jackson, Mich., for permission to examine two of the cases.

DISCUSSION.

Dr. Thomas D. Coleman, Augusta, Ga.: I have been impressed with the fact that the disease in question is very rare among negroes. These people are subjects of syphilis, tuberculosis and adventitious growths in general; but I have never seen a case of mediastinal tumor occurring in a full-blooded negro. I have seen two cases in mulattos. The other cases that I have seen occurred in whites and all the patients were males, aged somewhere between 30 and 60. One was a distinct case of carcinoma. The patient had had the pectoral muscles removed and finally succumbed to the disease, and the autopsy confirmed the diagnosis, cancer of the mediastinum. The chief point of interest in my cases, outside of the pressure and other symptoms, is that but one of my patients died. I had one case, the diagnosis of which was not verified, in which there was a distinct paralysis of the left vocal cord, which was supposed to be due to a gumma. The patient was placed on specific treatment with the result that recovery followed. The diagnosis in this case was fairly well established but could not be confirmed by the *x*-ray, as its use had not been discovered at that time, about eighteen years ago.

Dr. Alexander Lambert, New York: Some years ago I had a case that puzzled me very much. The lesion turned out to be a sarcoma which grew at the junction of the vena azygos major and the superior vena cava. The pressure symptoms were peculiar. When the patient was lying down he became blue from the clavicle up, the color of the rest of the

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body remaining normal; but when the patient sat up his face was white and he became blue from the clavicle to the hips. Whether lying down or sitting up the legs remained normal all the time. This tumor acted no doubt as a sort of ball valve. The diagnosis was made by working out the circulation of the chest wall. A primary sarcoma of the right ventricle of the heart was the original lesion. I have seen a number of mediastinal tumors at Bellevue Hospital, and what struck me as most interesting was that the symptoms came on paroxysmally, with a cough sometimes like that of whooping cough and without any apparent reason or cause of excitation. The pain and dyspnea came on paroxysmally. One symptom on which some stress was laid by the old English writers is the occlusion of the right innominate vein, which is pathognomonic of mediastinal tumors. This does not occur in aneurism.

Dr. Robert H. Babcock, Chicago: It was my fortune last summer to see a case of mediastinal tumor, the antemortem diagnosis of which was substantiated post mortem. The patient had been treated for pulmonary tuberculosis. This illustrates the fact that a physician may mistake for pulmonary tuberculosis a disease which produces a definite tumefaction of the front of the chest. It had been suggested to me, even before I saw the patient, that consumption might be present; but when I laid my hands on the front of the chest it was clear to me that this was not a case of pulmonary tuberculosis. Instead of a depression of the chest, a characteristic of the phthisical habitus, the upper portion of the chest was distinctly bulging, showing a condition of intrathoracic pressure.

Another interesting phase of the case was that the patient had been given mercury for syphilis for a long time. Certain sores in the mouth were thought to be mucous patches. The antisyphilitic treatment was pushed to the limit, but without benefit to the patient. A careful investigation of the history of this case revealed the fact that these sores were due to the mercury. This case was very instructive to me, because it showed conclusively the necessity of the physician entering carefully into the history of the case, and also the necessity of a clear discrimination between the symptoms of the various intrathoracic diseases, since if a diagnosis of intrathoracic disease is to be made, one should bear in mind the fact that it can not always be made by the physical signs alone.

Dr. John Francis Herrick, Ottumwa, Iowa: The diagnosis in these cases is very important. I have seen a case of aneurism of the posterior wall of the aorta in which the entire cavity of the aneurism was filled with a solid mass of fibrin before the patient was first seen. There was only a small opening through which the blood got to the aorta and left subclavian. The case appeared much like a tumor of the

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mediastinum, with pressure on the aorta. There was an absence of bruit. No information could be obtained from the history of the case. The diagnosis of a solid tumor was made, but an old aneurism, with its cavity filled with a solid mass of fibrin, was found at the postmortem.

Dr. Frank Smithies, Ann Arbor, Mich.: I am not quite certain whether my first case did not present quite as many symptoms of the Vaquez-Osler malady as it did of intrathoracic pressure. It becomes very interesting to consider the possibility of the blood changes being secondary to the long-continued intrathoracic pressure, with consequent hyperplasia of the bone marrow. Dr. Lambert's remarks about the paroxysmal character of the symptoms of mediastinal growths are interesting. With regard to the first case reported, the pupils were equal and active under ordinary conditions. During the paroxysmal attacks of dsypnea the right pupil became distinctly dilated, showing a certain involvement of the sympathetic. It seems to me likely that mediastinal tumors might really be differentiated ante mortem by means of radiograms.

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CLINICAL OBSERVATIONS ON ABSOLUTELY IRREGULAR HEARTS.

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The recent advances in our knowledge of the cardiac irregularities have enabled us to define their character and trace their inter-relationship with far more exactness than was ever possible before. The absolutely irregular heart,[1] in which all semblance to regularity has ceased to exist, is clinically the most important of the cardiac arrhythmias. It is less common, indeed, than are respiratory irregularities or extrasystoles; but it represents a far more serious condition, and James Mackenzie estimates that over 50 per cent. of all serious insufficiencies are associated with this irregularity. It is very important, therefore, that we should become acquainted with its characteristics, its clinical significance, and its relationships.

The distinguishing characteristics of the absolutely irregular heart will be discussed under three headings: (1) Absence of normal auricular contractions; (2) the irregularity itself, and (3) its permanency.

ABSENCE OF NORMAL AURICULAR CONTRACTIONS.

This is by far the most important characteristic of the absolutely irregular heart and one that denotes a fundamental change in the heart's activities. Our clinical evidences of auricular contractions, according to

1. This irregularity has been variously designated as the ventricular rhythm, nodal rhythm, rhythm of auricular paralysis, rhythm of the first Stannius ligature, perpetually irregular rhythm, etc.

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Mackenzie,[2] consist of (a) an auricular wave in the apex tracing just preceding the ventricular wave, (b) an auricular wave on the jugular and liver pulsations, and (c) the presystolic accentuation of the murmur of mitral or tricuspid stenosis. To these might be added (d) the presence of an auricular wave on the cardiogram obtained from within the esophagus,[3] and (e) the auricular wave on the electrocardiogram.[4] By none of these methods of examination has it been possible to demonstrate that the auricles contract before the ventricles in absolutely irregular hearts. Mackenzie was

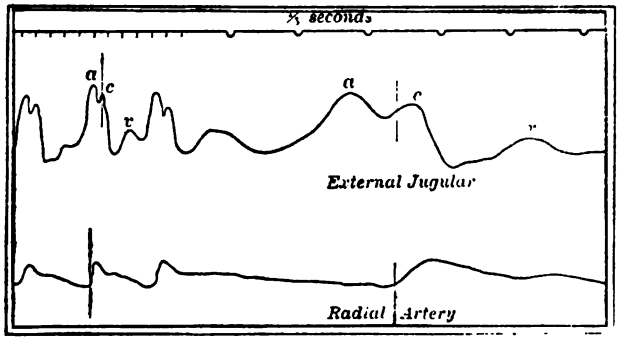

Fig. 1.—Normal venous pulse, showing the *a* wave preceding the *c* wave.

the first to insist on this fundamental fact. It is probably to be interpreted as a total auricular paralysis or at least as an auricular asthenia of such a grade that the contractions of this chamber are no longer demonstrable.[5]

The Venous Pulse in Absolute Irregularity.—In the normal tracing taken over the jugular vein the so-called *c* wave, which corresponds in time with the carotid

2. Mackenzie, J.: Abnormal Inception of the Cardiac Rhythm, Quar. Jour. of Med., I, 39.
3. Young and Hewlett: The Normal Pulsations within the Esophagus, Jour. of Med. Research, xvi, 427.
4. Kraus and Nicolai: Ueber das Elektrocardiogramm unter normalen und pathologischen Verhältnissen, Berl. klin. Wchnschr., 1907, 811.
5. Hewlett: The Interpretation of the Positive Venous Pulse, Jour. of Med. Research, xvii, 119.

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pulse, is preceded by an *a* wave due to the contraction of the auricle (Fig. 1). In similar tracings taken from patients with absolute irregularity the *a* wave is absent and the tracing rises abruptly without any preceding auricular wave (Fig. 2). It is now generally conceded that the first wave on such abnormal tracings, though corresponding in time with the carotid pulse, is not due to a transmitted arterial pulse, but is sent back into the vein from the heart.

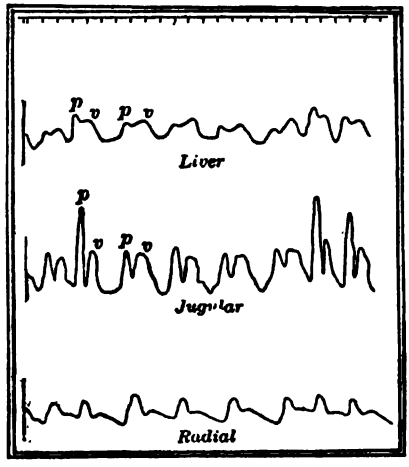

Fig. 2.—Venous and liver pulses of absolute irregularity, showing the absence of auricular waves.

I believe that this *p* wave[6] is due to the beginning of ventricular contraction. It can be demonstrated in tracings taken directly over the normally acting auricle, either internally from the esophagus[3] or externally when the bony chest wall is deficient.[7] In normal jugular tracings this wave is greatly diminished or absent because it is taken up by the diastole of the auricle; but when the auricular systole is absent, it is transmitted

6. Mackenzie's a′ wave. A similar wave on the normal venous pulse has been called the *s* wave by Bard, the *k* wave by H. E. Hering, and the *b* wave by Piersol.

7. Erlanger: Cardiograms Obtained from a Case of Operative Defect in the Chest Wall, Johns Hopkins Hosp. Bull., xvi, 394.

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back through the filled auricle and becomes a marked feature of the venous pulse.

Mackenzie believes that this wave is due to a contraction of the auricle simultaneous with that of the ventricle. It seems to me, however, that such an interpretation is unnecessary. When the auricle is known to contract simultaneously with the ventricle, as is the case in certain extrasystoles, the succeeding *v* wave is taken up by the dilating auricle and is diminished in size.[5] Such is not the case in absolute irregularity; but, on the contrary, the *v* wave is nearly always of unusual height. For this reason, especially, I believe that we are dealing here with a condition in which the auricle is motionless, or at least so nearly so that it does not affect the venous pulse.

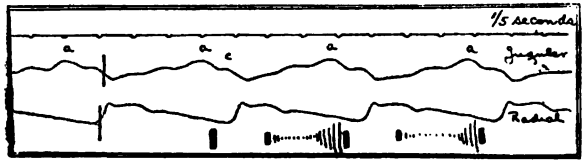

Fig. 3.—Normal type of venous pulse observed between the paroxysms of irregularity. The shading indicates the intensity of the mitral stenosis murmur. Figure reduced one-half.

A fourth venous wave, which occurs normally in late diastole, has been described by Hirschfelder, Gibson and others. A similar wave is occasionally very pronounced in cases of absolute irregularity. In some instances it seems to precede the next ventricular systole, and it might there be mistaken for an auricular wave. But, as a rule, it bears a constant time relation to the preceding ventricular systole so that it may be said to follow that rather than precede the next contraction.

Mitral Stenosis Murmurs in Absolute Irregularity.—Mackenzie has called attention to the remarkable change that takes place in the murmur of mitral stenosis when the heart assumes an absolutely irregular rhythm. The characteristic presystolic accentuation heard ordinarily is caused by the contraction of the auricle which in-

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creases the rate of blood flow through the constricted mitral orifice just previous to ventricular systole. When such a patient develops an absolutely irregular rhythm the mitral stenosis murmur may disappear entirely. If it persists it loses its presystolic accentuation. For the past two years I have paid particular attention to mitral stenosis murmurs in patients with absolute irregularity, and I have never heard a presystolic accentuation under these circumstances. The change from the normal was

Fig. 4.—Radial tracing during the paroxysm of irregularity. Figure reduced one-half.

particularly striking in the case of a patient who suffered from mitral stenosis with short paroxysms of irregularity. Ordinarily her heart was perfectly regular, and at such times her venous pulse was of the normal type (Fig. 3) and the murmur typically presystolic. From time to time, however, she suffered from short

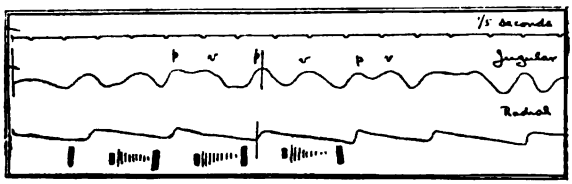

Fig. 5.—Venous pulse during the paroxysms of irregularity, showing an absence of the auricular waves. The shading indicates the intensity of the mitral stenosis murmur. Figure reduced one-half.

paroxysms of complete irregularity (Fig 4), during which her murmur lost its presystolic accentuation and her venous pulse became of the type ordinarily met with in absolute permanent irregularity (Fig. 5).

The absence of the presystolic accentuation of the murmur of mitral stenosis during absolute irregularity is a matter of decided diagnostic importance. Physicians should recognize the fact that a typical murmur at such a time is not to be expected. I could cite several

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case histories in which a mistake might have been avoided had this fact been kept in mind. In such patients the murmur, if present, is often heard throughout diastole. Frequently it has an early diastolic accentuation owing to the more rapid flow of blood through the narrowed orifice during the earlier and more rapid part of ventricular dilatation.

CHARACTER OF THE IRREGULARITY.

In typical cases of absolute irregularity the heart action is totally devoid of any semblance to regularity, a so-called delirium cordis. No two waves are of the same duration; rapid beats are followed by longer ones, and these in turn by a bewildering succession of pulse waves of varying duration and intensity. On auscultation over the heart the rhythm is often even more confused, for many of the shorter systoles produce no palpable radial pulses nor even second aortic sounds. Frequently we remark on the discrepancy between the number of heart beats and of pulse beats. The term delirium cordis expresses the extreme lack of rhythm. In other patients, however, the heart is comparatively slow, especially after compensation has been somewhat restored. I have seen it fifty-five per minute. The pulse is then fairly regular and every heart beat reaches the wrist. It may even, as in one of my cases, be perfectly regular for a time, though showing an absence of the *a* wave on the jugular pulse. Under these circumstances, however, the regularity is only transient and any light strain leads to a more or less definite delirium.

PERMANENCY.

The absolutely irregular rhythm is one of the most persistent arrhythmias. When once well established, it usually continues uninterruptedly until the death of the patient. As we have seen, the irregularity varies in degree from time to time and may be diminished by proper treatment. It may even merge into regularity

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for a while, but qualitatively it remains the same. The evidences of auricular contraction rarely return and slight strain is followed by a more or less marked delirium. The main exceptions to this characteristic permanency are the rather uncommon cases of paroxysmal irregularity, which will be discussed later.

ANALYSIS OF CASES.

Etiology.—This analysis is based on the histories of thirty patients who gave the typical tracings of absolute irregularity with absence of auricular contractions. The notes of these cases were often incomplete because many were seen only on account of the arrhythmia. Of twenty-four in whom the age was given, only five were under 40, fourteen were between 14 and 60, and five were over 60. The heart lesion most frequently encountered was mitral insufficiency. This occurred alone in ten cases, and associated with mitral stenosis in five more. Mitral stenosis alone was present in two cases, aortic lesions in three, and adhesive pericarditis in one. The remaining eleven cases showed no definite signs of valvular disease, and largely on account of the symptoms and character of the pulse they were designated as myocardial disease.

Among the etiologic factors in the past histories rheumatism stands pre-eminent, being present in twelve patients. The next most frequent factor, apparently, was the abuse of alcohol, being very marked in ten patients out of the thirty. Hyperthyroidism was the only demonstrable cause in two patients, chronic nephritis in one, while arteriosclerosis was noted in a number of others. It will be seen from these figures that absolute irregularity is most frequently associated with mitral valve disease, especially mitral insufficiency. It appears, however, to be relatively uncommon among younger patients, being more frequent in those over 40. Diseases that are known to cause changes in the heart muscle would also seem to be important causes of this irregu-

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larity, especially the abuse of alcohol, marked arteriosclerosis and hyperthyroidism.

Symptoms.—The symptoms of these patients represent all grades of heart failure. In the more severe types, dyspnea, edema and effusions into the serous cavities were common. About a third died or were permanently and totally incapacitated for any effort. In the less severe types the symptoms were less marked. Indeed in two patients no symptoms whatever were complained of. One of these worked as a gardener without any apparent inconvenience except on extreme exertion. The other was a prospector who boasted of his ability to endure hardships and long excursions into the mountains. It is apparent, therefore, that a moderate degree of irregularity associated with auricular paralysis is not enough in itself to cause severe symptoms. This seems to be especially true when the irregularity is unassociated with valvular disease.

On the other hand, it undoubtedly adds to the gravity of the situation. The circulation can not be so good when the heart is contracting irregularly. The effect of the auricular paralysis independently of the irregularity is difficult to estimate, but Henderson's studies[8] would seem to indicate that the auricles play a less important part in the normal filling of the ventricles than is generally supposed. The effect of the irregularity is well illustrated in the case of paroxysmal arrhythmia already referred to, for the paroxysms caused this patient to suffer from precordial distress and decidedly increased dyspnea on exertion.

Relation to Tricuspid Insufficiency.—The relation of absolute irregularity to tricuspid regurgitation is of great importance, but it can not be defined with exactness at the present time. That many of these patients do suffer from tricuspid insufficiency is evidenced by the typical murmur, the positive plateau on the venous pulse, and the positive pulsations of the liver. In not a

8. Amer. Jour. Physiol., xvi, 325.

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small number, however, especially after compensation is moderately restored, the liver ceases to pulsate and no murmurs whatever can be heard over the heart. In such cases the only possible evidence of tricuspid insufficiency is the positive venous pulse. Since the time of Riegel's[9] paper in 1881 this has been regarded by many as a pathognomonic sign of tricuspid insufficiency; but, in my opinion, we are not justified in diagnosing tricuspid insufficiency in such cases, for the abnormal venous pulse may be explained solely on the assumption of an auricular paralysis.[5]

Enlargement and tenderness of the liver was noted in a large proportion of my patients. In many the liver could be felt at the level of the umbilicus and pulsated vigorously during the stages of broken compensation. As compensation returned the tenderness and pulsation often diminished or disappeared and at the same time the liver became smaller. Most, if not all, of these cases were associated presumably with tricuspid regurgitation.

RELATION TO PAROXYSMAL IRREGULARITY.

Delirium cordis may occur in paroxysms which last but a few hours or days. The subject has been reviewed recently by Cushny and Edmunds[10] and by Hornung.[11] The following case presents a good example of this form of irregularity:

History.—Mrs. B., aged 55, was referred to me on account of an influenza and a right-sided hemianopsia. Her family history was negative. She had suffered from four attacks of facial paralysis at different times in the past thirty years, the first being on the right side and the remainder on the left. The last occurred in 1906 and was very mild. She never had acute articular rheumatism. In June, 1906, she was treated for heart disease, which became so bad a month later that she was unable to sleep in a recumbent position on account

9. Ueber den normalen und pathologischen Venenpuls, Deut. Arch. f. klin. Med., xxxi, 1.

10. Paroxysmal Irregularity of the Heart and Auricular Fibrillation, Amer. Jour. of the Med. Sci., cxxxiii, 56.

11. Ueber atypische tachykardische Paroxysmen, Deut. Arch. f. klin. Med., xci, 469.

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of dyspnea. Since then she had had several moderate breaks in compensation with dyspnea, cardiac distress and at times slight edema. In the intervals her compensation had been fairly good. In June, 1907, she was suddenly seized with weakness in the legs. Immediately after the seizure she noticed that the right leg was insensitive to touch, to pinches, and to the heat of a hot-water bottle. The weakness disappeared from the left leg almost immediately, but the right remained weak for several days. The disturbances of sensation also gradually passed off, and at the end of ten days she had completely recovered. Her rectal and bladder functions were not affected. On Dec. 1, 1907, while riding on a street car, she sustained an emotional shock, and her ideas became so confused that she was unable to find her way home without slight assistance. At dinner she noticed for the first time that she was unable to see objects to her right. She also had some headache for the next forty-eight hours, but no nausea or vomiting. I was called to see her Feb. 3, 1908. An epidemic of influenza had been passing through the household and she was suffering from the usual symptoms of this infection. In addition, she presented the typical signs of a mitral stenosis. She was also found to have a right-sided hemianopsia, more marked in the upper quadrant. Subsequent examinations showed a gradual improvement in the fields of vision until when seen the area of total blindness was limited to a small spot in the upper right quadrants of both eyes. Her hemianopsia was probably due to an embolus in the right occipital lobe. Probably also the transient paraplegia was due to a slight embolic process in the lower cord.

Examination.—On my first examination the pulse was 80 per minute and perfectly regular. The mitral stenosis murmur was of a marked presystolic type, with little if any rumble in early diastole (Fig. 3). Three days later, after her temperature had fallen to normal, she complained of precordial distress and felt unusually weak. The heart action was found to be absolutely irregular and about 120 per minute (Fig. 4). The mitral murmur had completely changed its character. Its presystolic accentuation had disappeared, and it was now loudest just after the second sound and in the longer diastolic intervals it practically disappeared before the occurrence of the first sound (Fig. 5). The following morning the heart action was again absolutely regular and 85 per minute, and the murmur had returned to its customary presystolic type. The early diastolic portion of the murmur was almost inaudible. The precordial distress and general weakness had passed away.

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Subsequent History.—Since that time the patient has had about seven of these paroxysms of cardiac irregularity, and I have been able to observe her in three of these. These seemed to begin abruptly and were induced more especially by emotional disturbances, e. g., by seeing a dog nearly run down by a street car. Other attacks seemed to follow physical exertion. The attacks usually lasted during the day and passed off during the following night, the termination often being associated with sweating. During the paroxysms the patient felt weak, short of breath on exertion, and suffered considerable distress from cardiac palpitation. Examination of the heart during the paroxysms showed a slight enlargement of the cardiac dulness, and an absence of the presystolic accentuation of the mitral stenosis murmur. Between attacks her venous pulse was of the normal type, with a fairly prominent auricular wave (Fig. 3), while during the

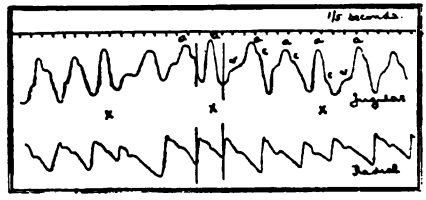

Fig. 6.—Venous pulse on the day following a paroxysm of irregularity, showing the frequent occurrence of auricular extrasystoles. Figure reduced one-half.

attacks no sign of an auricular contraction could be discovered in the jugular pulse (Fig. 5). It seems fair to assume, therefore, that during these paroxysms her auricles had ceased to contract normally.

Cushny and Edmunds[10] have suggested that such attacks may be due to fibrillation of the auricles. In the case of our patient this hypothesis receives a certain amount of support from the fact that on the day subsequent to one attack numerous auricular extrasystoles were observed (Fig. 6), indicating that the auricles were abnormally irritable.. Mackenzie believes that such paroxysms may be due to an abnormal irritability of the node at the upper portion of the His bundle, which may take on the function of initiating the cardiac rhythm.

The exciting causes of the paroxysms in our patient were, as a rule, excitement or exertion. Hornung[11] has

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also noted psychic causes of such paroxysms. In one of his patients the irregularity frequently accompanied defecation, but finally it would be induced when the patient merely started for the toilet. Fr. Müller[12] refers to patients in whom paroxysms were caused by overloading the stomach and were relieved by vomiting or lavage. Although it seems probable from these observations that such paroxysms of irregularity may be induced by nervous influences, nevertheless some other factors are probably present which render certain hearts susceptible to such nervous influences. Hornung emphasizes the arteriosclerosis in three of his four patients, and mitral valve disease was present in both of mine.

The relation of such attacks of cardiac arrhythmia to the permanent form of absolute irregularity is probably an intimate one. In my patient the paroxysms were associated with auricular paralysis just as is the case in the typical permanent form. Paroxysms have also been noted in patients who subsequently developed a permanent delirium. One of mine had been admitted to the hospital several years before with delirium cordis. This had disappeared after a few days, as was shown by the radial tracings taken at the time. At present he suffers from typical permanent irregularity.

RELATION TO TACHYCARDIA.

There is a form of tachycardia which is associated with a positive venous pulse with absence of auricular waves. This may be of the paroxysmal type with a normal venous pulse between the paroxysms or it may occur when evidence of auricular contractions is permanently lacking. The latter is certainly closely related to the permanent form of absolute irregularity, and several observers[2] have noted that the two may alternate in the same patient. I have observed a sudden change from tachycardia with a positive venous pulse to the abso-

12. Müller, Fr.: The Nervous Affections of the Heart, Arch. of Int. Med., 1, 1.

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lutely irregular pulse. This patient who had myocardial disease was given an intravenous injection of one milligram of strophanthin. Within a few minutes his pulse changed from a regular rate of about 150 per minute (Fig. 7) to an absolutely irregular pulse of about 70 per minute (Fig. 8). At the same time his symptoms improved greatly. Since that time his pulse has been for the most part absolutely irregular, though at times it shows a tendency to return to the tachycardia that was present when he was first seen. The relation of paroxysmal tachycardia to the irregularities under discussion is

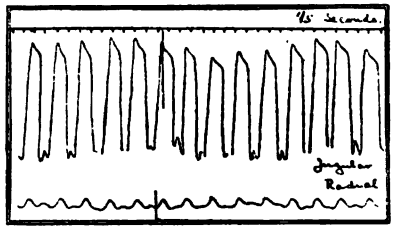

Fig. 7.—Tachycardia with positive venous pulse before strophanthin injection. Figure reduced one-half.

less certain, but Hornung[11] has seen a paroxysmal irregularity pass directly into a paroxysmal tachycardia so that there seems some justification for grouping the latter close to the absolute irregularities.

THE EFFECT OF DIGITALIS AND ATROPIN.

It may be said in general that digitalis and atropin have much the same effect on absolutely irregular hearts as they have on normal hearts. Atropin increases the heart rate and digitalis slows it. Mackenzie[2] is of the opinion that digitalis acts especially on those irregular hearts which are associated with mitral valve disease, but I have seen similar results follow its use in patients with myocardial disease. The most striking digitalis effects are produced by the intravenous injection of strophanthin, for here the change in heart rate occurs within a few hours, and other accessory factors, such as

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rest in bed, can be eliminated. In addition to slowing the pulse digitalis usually renders it less irregular, increases its size and improves the subjective and physical condition of the patient. In my experience, however, neither digitalis nor atropin have ever caused the pulse to return to a normal character.

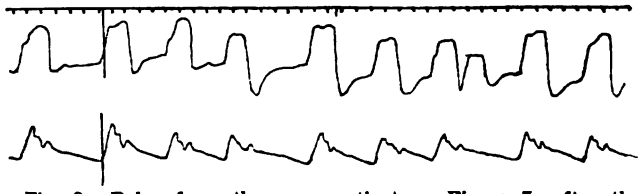

Fig. 8.—Pulse from the same patient as Figure 7, after the strophanthin injection; a typical absolutely irregular pulse.

DISCUSSION.

Dr. Robert H. Babcock, Chicago: During the last few years Mackenzie's work has revolutionized our ideas of cardiac arrhythmia, and much work has been done by others also. The great difficulty lies in the fact that the use of the instruments by which the heart's irregularity is determined is difficult, and in fact belongs to the expert. It requires an expert to obtain good jugular tracings, as well as to interpret the tracings obtained. The fact remains, however, that we are to depend on the use of instruments in the diagnosis of cardiac disease, not only in recognizing cardiac disease but also to aid in deciding on the therapeutics appropriate in cardiac disease. For it is evident that when there is some serious interference with the transmission of stimulus to contraction from venous sinuses to ventricles with a disturbance in the cardiac rhythm of one kind or another, certain medicines, such as those belonging to the digitalis group, are not beneficial but actually dangerous.

Dr. Arthur D. Hirschfelder, Baltimore: Paralysis of the auricles was first demonstrated experimentally on animals by von Frey and Krehl in 1890 and subsequently on man by Mackenzie in about 1894 by means of the venous tracings. The absolute demonstration, however, was not really decisive until Dr. Hewlett demonstrated it by means of a tracing from the esophagus. Prior to this it might have been possible for a weak auricular contraction to go on without registering on the venous pulse; but now comparatively small contractions can be recorded in these excellent esophageal tracings. Therefore, it would appear as demonstrated almost beyond a shadow of a doubt. Auricular paralysis is very commonly seen in experiments on animals. In fact one can

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hardly experiment on exposed hearts without finding paralysis of the auricle at some period or other during cardiac failure. No trace of fibrillation can be seen under these conditions in any part of the auricle. Clinically I can only agree with Dr. Hewlett's findings. I have found transitory periods of auricular paralysis, etc., with absolute irregularity in cases of mitral stenosis; and disappearance of the presystolic auricular rumble at these times. I have been able to obtain the same thing in animals in experimental mitral stenosis. When mitral stenosis is brought about slowly, I have obtained, first, a gradual slowing in the diastolic filling of the heart. After the production of a more marked stenosis diastole was divided into three periods: First, a period of rapid filling; a second period, in which there was a little further filling; and a third period marked by contraction of the auricle. About one-half of the filling of the ventricle was due to this contraction of the auricle, as compared with about one-fifth in the normal heart. The presystolic rumble was loud under these conditions. If the mitral stenosis was further increased, auricular paralysis set in, arrhythmia also appeared, and the presystolic rumble disappeared. In other words, a large part of the filling of the heart was due to auricular systole and also led to a presystolic rumble and later, when auricular paralysis appeared, the auricular sounds disappeared. Clinically, I have been able to find sounds similar to those described by Dr. Hewlett as a diastolic murmur. This was particularly true in one case, in which I was able to hear a soft blowing murmur throughout diastole heard at the apex and along the left border of cardiac dulness, and also just above the angle of the scapula, corresponding exactly to where one would expect to hear if it was produced in the left auricle.

Dr. W. S. Thayer, Baltimore: I feel that the term "presystolic" murmur applied so commonly in literature in a general way, to the mitral diastolic murmur, is rather unfortunate. As a matter of fact, heart murmurs heard in mitral stenosis vary greatly in character. 1. One may hear at the apex of the heart a characteristic rumbling murmur limited to that part of diastole immediately preceding systole; that is, to the time of the auricular contraction. 2. The murmur may begin shortly after the second sound with marked presystolic accentuation. 3. The murmur, of fair intensity, may begin shortly after the second sound, which diminishes in intensity during the middle, to increase again at the end of diastole. 4. The murmur may begin shortly after the second sound, disappearing entirely during a good part of diastole and reappearing again at the time of auricular contraction. 5. The murmur may be observed to begin closely after the second sound and to disappear entirely before the period of auricular systole. In all these cases in which the murmur begins in the early part of diastole it is usually ushered in by a slight

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snap, the so-called "opening snap" of mitral stenosis, probably due to the early tension of the sclerotic and adherent mitral valves. 6. One may hear only the first and second sounds and the opening snap without murmurs. 7. One may hear no adventitious sounds whatever in the long pause. It is then by no means uncommon for a mitral diastolic murmur to occupy a position in the cardiac cycle other than that of presystole.

Dr. Edward F. Wells, Chicago: Any one who studies the cardiac rhythms will find them very suggestive, and I have studied them for many years. Some very curious features have cropped out in these investigations. For instance, the heart at one time may have presented a fairly regular rhythm, but as time goes on irregularities of the heart become more common, if not the rule. As pointed out, the paroxysmal character of the arrhythmia may be extremely marked. For example, in tachycardia the rhythm is usually irregular, sometimes very much so. This same applies, but to a much lesser degree, to paroxysmal bradycardia. I have under observation at the present time a man 75 years old with paroxysmal irregularities of the heart; these paroxysms are very profound and accompanied by cardiac distress, coldness of the skin, perspiration, etc. In this case it was noticed several years ago that efforts at vomiting would relieve the paroxysms. Although the pulse is rapid and might be classed as paroxysmal tachycardia, still the irregularity is so great that it belongs to the category of paroxysms of irregularity of the heart. In this patient, aside from marked arteriosclerosis, nothing could be found to account for these irregularities. There are other forms of irregularity, with tachycardia or bradycardia, in which the preceding features were very suggestive. For example, I have under observation one case, a woman, whose occupation requires her to lift heavy objects above her head. Her attacks are frequent and are brought on by this heavy lifting. Sometimes the attacks are short, sometimes prolonged. I have another patient under observation with paroxysmal bradycardia in whom the attacks may be induced by suspended respiration.

Dr. R. C. Allen, St. Joseph, Mich.: There is one fact that evidently has been overlooked; that is, that many of the symptoms described are often the result of reflex phenomena rather than of organic disease of the heart. I do not refer to any special cases. In many cases it is difficult to draw a line between the many forms referred to, whether they are due to organic disease of the heart or to reflex disturbances or irritation. This is a fact very well illustrated by the last speaker. His cases might have been reflex in origin. I have a case in which there is a purely neurotic cause, a result of reflex irritation. This is a fact which I consider important and worthy of consideration. In these cases of mere

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tachycardia, with difficulty of respiration, etc., I would place the patient on morphin, bromid of potassium or similar agents, and the symptoms would abate.

Dr. G. W. McCaskey, Fort Wayne, Ind.: It seems to me difficult to demonstrate positively the occurrence of auricular paralysis. The absence of tracings by the intra-esophageal method is perhaps very nearly conclusive, beyond which it is impossible to entirely exclude weak and inefficient contractions of the auricle. I wish to call attention to the importance of the use of the stethoscope simultaneously with the graphic methods, as well as in the study of presystolic murmurs as a further evidence of auricular paralysis. The stethoscope is valuable in those cases in which the ventricle has apparently failed to contract in consequence of an inefficient auricular contraction or functional impairment of conducting fibers. Where there is no radial pulse and no palpable apex beat by means of the stethoscope, I am sometimes able to distinguish inefficient contractions, which would produce no pulsation whatever.

Dr. A. W. Hewlett, San Francisco: Experimental observations in regard to the production of auricular paralysis with absolute irregularity have been limited to acute conditions, whereas the clinical form of absolute irregularity is chronic and this has not yet been produced experimentally. I agree with Dr. Thayer regarding the various forms of the murmur of mitral stenosis. The presystolic accentuation when present denotes that the left auricle is active. This accentuation is absent when the pulse becomes irregular, thus adding one link to the evidence that shows that the auricle is not contracting to any demonstrable extent.

The prognosis of absolute irregularity depends on whether the condition is a paroxysmal or permanent one. If the former, the attack may be terminated by some obscure reflexes just as it may be initiated by such reflexes. If the latter, I know of nothing which will cure the irregularity. We can merely hope to improve the condition of the patient.

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PHYSICS OF PHYSICAL SIGNS, WITH SPECIAL REFERENCE TO THE RESPIRATORY MURMUR.

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In these days of modern scientific medicine the study of physical signs is not receiving as much attention as it deserves. Scientific medicine stands essentially for two things: accuracy of observation, and the basing of conclusions on facts rather than on assumptions or theories. We view with pride the advances in our knowledge of medicine acquired by work along these lines, and pride is justified when we compare our knowledge to-day with that of even a few decades ago. But we are mistaken if we assume that medicine has already attained the rank of a science, for we have as yet made only a few steps in that direction.

Unfortunately our knowledge of physical signs has lagged far behind many other branches of medical knowledge. It is far from deserving the term "scientific," and it has fallen into disrepute which is more or less well deserved. The scientific investigator avoids this chaos of empiricism and is attracted to other fields in his research work—the more the pity, for we need his help most where the darkness is greatest. And yet this is one of the most important fields of medicine. We must make our diagnosis before our patient is a proper subject for investigation by the pathologist, and the laboratory worker can as yet solve only a few of the

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troublesome problems of diagnosis. In a large majority of cases we must still depend on our study of the sick patient himself, by the use of our own senses aided by a few instruments of precision.

One reason for the disrepute of physical signs is that we do not sufficiently train our senses to keenness of perception. Again we fail to appreciate fully that these signs are based on the laws of physics, and we are too often oblivious to the distinction between facts and fancy in our explanations. Until we rid physical diagnosis of these defects—imperfect or inaccurate observations, theories in place of facts, explanations that are both illogical and inconsistent with the known laws of science—it deserves the disrepute in which it is held by scientific minds.

Many of these illogical and ill-founded statements are hallowed by tradition. They were accepted by us as matters of course. They have become familiar by frequent use in the practice of medicine and stand in our estimation as established principles or facts chiefly because we have never questioned them critically. How many of them will stand close scientific criticism? The number that fail to meet these requirements is surprising.

Although our recent text-books on physical diagnosis are making some efforts in the right direction, they are still handing on many of these faulty traditions from generation to generation of medical students without even intimating that they are open to question. The text-books are open to severe criticism because they thus fail to discriminate between unfounded theories and established facts or well-grounded hypotheses. It is true that our knowledge of physical signs can not now be reduced to a satisfactory scientific basis, and that there are many problems that the science of physics is not yet prepared to solve. It is true that the medical men are not well enough trained as physicists to solve many of the problems and that the physicists are not

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working in this direction because they do not know what the problems are and do not realize their importance. We shall need highly trained physicists to help in the solution of many of these problems, just as we are now utilizing the services of highly trained chemists to investigate the problems of metabolism. But there is no need of waiting for this era of the future before making a beginning of our housecleaning. We can at least discard statements that are clearly inconsistent with the simplest principles of physics. In many cases we can estimate the degree of doubt about statements now accepted as truths. If an hypothesis is reasonable enough, we can accept it as such and use it as an aid in the search for truth. In this way we can at least determine more clearly some of the problems we want science to solve.

I believe that this is a most important matter in the future development of scientific medicine—a thing we shall never have until the methods in clinical medicine are scientific. At present we train students in the laboratories of the college and medical school to accurate, critical observation and to logical reasoning in accordance with the laws of science. But when we teach physical diagnosis—the foundation of clinical medicine—we pay little attention to scientific methods.

To illustrate these faulty methods I have chosen the respiratory murmur for consideration, although many other topics would make equally good examples. We are dealing with phenomena of sound. In the textbooks the characteristics of the sound or murmur, as heard at various places on the chest, are described with fair accuracy. These sounds are compared as to quality, intensity, pitch and duration. The difference between the inspiratory sound and the expiratory sound at a given place is noted. The recording of isolated facts is fairly well done.

The recognition of two types of breathing sound is the first generalization from these facts and is too

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obvious to cause dispute, but serious differences of opinion arise as soon as we attempt to explain why there are two types. This leads to questions as to how and where the sound originates; and opinions, theories and assumptions are bandied back and forth by the best authorities with little regard for facts or the laws of physics. And yet the answer to these questions could be determined by experiments more easily than the physiologist learns about the digestive processes.

In the absence of such proof by experimental evidence we have only hypothesis or assumption; we should offer it as such and not as an established truth. For example, there are two opinions as to where the inspiratory murmur originates. According to one, it originates only at the glottis and all modifications are due to changes caused as it is transmitted through the lung tissue. The other opinion agrees that one type of the inspiratory sound originates in this way, but maintains that the second type originates in the minute air spaces of the lung. High authorities may be found in favor of each of these two views, and the question can not be regarded as settled. But often the text-book cites one opinion as if it were an established truth and does not even mention the existence of the other.

When there exists such a difference of opinion among the best authorities this fact should be stated, and the text-books should decide in favor of one view or the other. It should make this decision because in its opinion the view accepted is more nearly in accord with known facts and scientific principles, and it should give its reasons fully. I do not know of a text-book that gives more than an imperfect exposition of this matter. These publications rely chiefly on authority and not on demonstration to prove points.

Neither do any of the text-books discuss intelligently the transmission of the sounds from their points of origin to the surface of the chest. It is but a matter

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of the applied physics of sound. We can understand it best by adopting the attitude of the physicist. He thinks only in terms of vibrations—of matter in motion. He recognizes the fact that sound vibrations exist at the surface of the chest in association with rhythmic breathing. He asks these questions: What causes these vibrations? Where do they originate? How are they transmitted from the point of origin to the point where they are heard?

If our text-books are to teach physical diagnosis scientifically, they must adopt these same methods and teach the physics of physical signs. In this paper the limitations of time compel me to do exactly what I criticize the text-books for doing—to state my position on doubtful problems without giving reasons. However, as I am now contending for methods of study and teaching and not trying to establish facts, I may be excused for not practicing what I preach.

The answers to the first two questions of the physicist are as follows: The vibrations arise at two places—the glottis and the point where the minute bronchus opens into its air sac. The cause is the passage of air with sufficient force through a narrow opening into a wider space beyond—it being a general principle of physics that under such circumstances the air is thrown into vibration as it emerges into a larger chamber. It is easily understood that the intensity of vibrations at the glottis should be great enough to make them audible, but a word of explanation is needed as to the other source of sound. The immense number of the air sacs which contribute vibrations cause an audible sound when the vibrations from small numbers of the sacs would be inaudible.

We now come to the study of the way in which the vibrations are transmitted from these points of origin to the surface. It will not be out of place to recapitulate some of the principles of the physics of sound that

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are involved in this study. From the point of view of the physicist, sound is a form of energy, existing in the form of vibrations of matter. These vibrations are of such a character that they are capable of being perceived by the sense of hearing, provided they have a sufficient intensity and the rate of vibration falls within certain limits. In studying the transmission of these vibrations, then, we are studying the transmission of a form of motion from one set of particles of matter to another set. If these particles of matter are uniform, that is, if there is a uniform medium, the vibrations will travel in all directions at a uniform rate for that medium, but will lose in intensity as the square of the distance. Different media will transmit the vibrations at different rates and may accordingly be classified as good or bad conductors. Sound vibrations are more or less reflected when in the course of their transmission they come to a boundary between two media. Sound vibrations are also more or less refracted within a medium of uniform consistency but irregular extent. These principles of the reflection and refraction of sound vibrations cause the vibrations to travel more easily within the confines of any anatomic structure than to be transmitted to surrounding structures. Bodies of uniform, elastic structure are especially good conductors. Soft, relaxed tissues, like membranes, which are poor conductors, may become good conductors if they are put on the stretch.

It follows that the vibrations will travel a certain distance in all directions from their point of origin, depending on their intensity at the start and on the conductivity of surrounding tissues. They will travel better and farther in certain directions, which will be determined by the anatomic shape, the consistency, elasticity and tension of the structures that are thrown into vibration.

Let us consider first the vibrations originating during

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inspiration in the air sacs. They originate throughout the lung structure. They have intensity enough to be transmitted to the overlying chest wall, if it is in direct contact with the lung tissue, and will be carried by an ordinary chest wall to the surface with intensity enough to be heard by the ear. The intensity, however, is not sufficient to carry the vibrations on the surface far beyond the anatomic limits of the lungs, nor can they reach the surface if anything intervenes between the lung and the chest wall.

In case of vibrations originating at the glottis during inspiration, the problem is a little more complex. There are two sets of vibrations—those originating in the air column itself, and those originating in the vibrating vocal cords. The vibrations in the air column will be transmitted down the air of the air passages as in a speaking tube, and the vibrations from the vocal cords find their best line of transmission along the walls of the air passages. Both these lines of transmission (air conduction and tissue conduction) are good so long as the bronchi are of moderate size and have stiff walls. In other words, the glottic vibrations are conducted throughout the inner part of the lung as far as the smaller bronchi extend. Between this point and the surface lies a more or less thick layer of lung parenchyma, which, with its minutely divided air spaces, is a poor conductor of vibrations. The glottic vibrations are distinctly audible at the surface over a thin layer of lung and the intensity diminishes with the thickness until it entirely fails to penetrate the thickest part, where we hear only the vesicular murmur. At intervening points we get a combination of the two types of breathing sound, and the predominance of one or the other is determined at any point by the anatomic relations beneath.

Let there be a little thickening of the lung tissue—as in the earliest changes of tuberculosis—and the

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laryngeal sounds are better conducted through the lung. The laryngeal element is found to be stronger than it normally would be at that point. This increases in proportion to the density of the lung tissue until with a solid area of the lung extending from the surface to the bronchi we get pure bronchial sounds.

Let us now consider the expiratory murmur. During expiration no suitable conditions exist in the lung parenchyma to cause audible vibrations and the vibrations come only from the glottis. Here the air is thrown into vibration as it rushes from the glottis into the pharyngeal space above, but these vibrations are practically all cut off by the vocal cords from reaching the air passages of the lung. The audible vibrations, therefore, come almost exclusively from the vibration of the vocal cords. These vibrations are transmitted (as in the case of inspiration) by tissue conduction through the walls of the air passages to the interior of the lung. They have not volume enough easily to penetrate the lung tissue. When, however, at the beginning of expiration the lung tissue is on the stretch these vibrations are faintly audible at the surface, but they become inaudible as soon as the lung loses this tension. The result is that over the thicker lung tissue the expiratory murmur is only a short puff at the beginning of expiration.

Let the lung tissue be slightly thickened, as in early tuberculosis, and there is better conduction of vibrations through it. The expiratory murmur is a little louder and longer. This increases with the density of the lung until with a consolidated lung there is a full bronchial expiratory sound.

With such an explanation of the respiratory murmurs, based on a consideration of the physics of the vibrations in the lung tissues, one gets an understanding of the complex combination of sounds in health and readily translates the variations that come with disease

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into terms of changes in the texture of the lung tissue. This is the real aim of auscultation of the respiratory murmur—to learn the texture of the lung tissue.

I do not claim that this explanation of the respiratory murmur is necessarily correct. It is based on hypotheses, not on facts proven by experiment, but it is consistent with the laws of physics and offers an intelligent basis from which to carry out further investigations which will confirm or disprove it. It is by steps of this sort that we shall advance to the truth, shall remove the opprobrium from which physical diagnosis now suffers, and shall introduce scientific methods into clinical medicine.

DISCUSSION.

Dr. George N. Jack, Buffalo: Many cases of asthma have been sent to me diagnosed as bronchial asthma. On careful investigation I would find the obstruction to be confined wholly to the common air tube, the bronchi being entirely free of all râles or signs of obstruction. As the condition in the larynx would clear up the dyspnea and wheezing would disappear. I know of no other way to explain how through all ages asthma could have been classed as a nervous spasm unless the mistake was due to the transmission of sound from the trachea-larynx to the bronchi. The condition is not a nervous spasm, but is due to an obstruction in the air tubes. For the last ten years I have alone maintained that asthma is not due to a nervous spasm of the air tubes, and very recently Gee of Oxford (in the Gee Medical Lectures, 1908, pages 140 and 160) has taken the same stand. The real or severe dyspnea of asthma originates from a plugging of the common air tube which no one would accuse of spasmodically contracting. When the obstruction is in the smaller bronchi and the common air tube is open, asthmatics will breathe quite freely with little dyspnea; in fact, they can at such times exert themselves with little dyspnea when the chest is full of râles of all sorts as the numerous small bronchi are never all plugged at the same time. Can there, then, after considering the facts in regard to respiration that Dr. Arnold has brought out, longer be any excuse for asserting that a wheeze that can be heard clear across the street can come from the small bronchi way down in the chest?

Dr. Henry Sewall, Denver: I believe that the terminology used in expressing the findings of a physical examination, such as calling the sounds heard "moist" or "dry," is too much restricted to denoting the subjective impressions aroused,

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which differ for every examiner, and too little descriptive of the objective physical conditions in the field. It is highly desirable that our armamentarium be enriched with devices which shall limit the range of the personal equation. Some years ago I carried on some experiments in this field with interesting practical results. It will be admitted that the sounds perceived in auscultating the chest owe their intensity to two sources: first, the vibrations of the tone-producing body, which may be conducted to the ear according to known physical laws; and, second, sympathetic vibrations which depend on the elastic properties of the media surrounding the vibrating body and which more or less reinforce the original vibrations; indeed, in certain sound productions, as in human vocalization, the resonance sounds far outstrip in intensity the unaided vibrations that give them birth. To be brief, the resonance tones of the chest wall can easily be damped and deadened. The remaining sounds are those that come by direct conduction from the vibrating body. This feat can be achieved by use of the ordinary binaural stethoscope having only air conduction between the bell and the ear tubes. Apply such a stethoscope over the aortic area and the second sound of the heart may be heard of great intensity. If the bell of the instrument be now pressed firmly into the second right interspace the sound nearly or completely dies away. That is, the second sound, as heard in the aortic area, owes its intensity to sympathetic vibration of the chest wall. On the contrary, if the stethoscope is applied to the area of the cardiac impulse, where the vibrations are conducted directly to the instrument, no amount of pressure does away with the heart sounds. I have found in "stethoscopic pressure" perhaps the most accurate means of outlining the borders of the heart, a feat which is frequently so difficult. It is interesting to observe that an instrument depending wholly on air conduction is necessary to the success of this method. If the original wooden, monaural stethoscope is used, increase of pressure, for example, in the aortic area, does not deaden the sound, for reasons that are obvious.

Dr. Walter E. Scott, Adel, Iowa: One important factor in the production of the respiratory murmur has been omitted, namely, the sound produced by muscular contraction of the muscles used in respiration, the so-called "muscular murmur." The contraction of muscles is always accompanied by the muscular murmur, and the great number of muscles used in respiration is no exception to the rule. I am at a loss to understand how the consideration of the muscular murmur could have been omitted in mentioning the sounds originating within the chest, especially when one takes into consideration the great number of muscles attached to the chest and to the ribs. It is easy to observe the murmur produced by muscular contraction and to prove that it plays

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a large part in the production of the vesicular respiratory murmur. If one closes the external auditory canal with the finger tip the roaring sound heard is the sound of the muscular contraction of the muscles of the hand and arm, as is proved by the fact that the sound is absent when the ear is closed with wood, hard or soft rubber, etc., and that the contact of the fingers with the stethoscope produces the same sound. The word "murmur" at once indicates that the vesicular-respiratory murmur might be made up partly of this muscular murmur. With the tip of the finger in the external ear it is easy to familiarize oneself with the muscle sound and then by listening to the chest to discern the muscular murmur as being a part of the vesicular murmur. The muscular murmur is a large part of the vesicular respiratory murmur. If muscle contractions always produce such murmurs, is it not wise that we should consider this sound as a part of the sounds originating within the chest? It is, in my opinion, very reasonable to conclude that a considerable part of these sounds are due to this muscular murmur. Dr. Arnold stated that these vesicular sounds went directly to the surface, while Dr. Scott, in reply, said that the muscles were, for the most part, attached to the ribs and the sounds referred to originated near the surface. Dr. Arnold also stated that in expiration all the vibration originated in the glottis. It should be remembered that in expiration there is no action of the muscles; they are not contracting, but relaxing. Therefore, there is an absence of the muscular murmur, and that part of the vesicular respiratory murmur is absent, except at the beginning of expiration, when the lung tissues are on the stretch. But with inspiration the muscles are at their highest tension, and the intensity of the muscular murmur is largely to be noticed. The vesicular murmur has two factors in its production—one the muscular murmur, the other that caused by the passage of air in the lungs. The worthy Chairman of this Section, at the Saratoga meeting, a few years ago, read a paper on this subject and related a case in which the patient hiccoughed for a number of hours each day until his death. Dr. Hoover proved conclusively that, when the glottis was firmly closed and no air was entering the lungs, the vesicular respiratory murmur was still present. If that is true the vesicular respiratory murmur does not originate in the vesicles, but is explained by the sound of muscular contraction.

Dr. H. D. Arnold, Boston: The object of my paper is to stimulate the clinician to think. To-day men should be more imbued with the spirit of scientific research and scientific thought; then they would work and make some advance in the study of disease, the same as the laboratory workers have done, and then they would be a greater credit to modern medicine.

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RECENT STUDIES ON THE CIRCULATION AND THEIR IMPORTANCE TO THE PRACTICE OF MEDICINE.

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The contributions to our study of the circulation during the past few years have been so numerous that I shall be able to deal only with a few of those aspects in which I have been most directly interested and which I feel are of practical importance; namely, the relation of arrhythmias and of the velocity coefficient to treatment and the studies on the volume and tonicity of the ventricles.

One of the most interesting and important results of physiologic study has been the physiologic analysis of the irregular pulses, which has led us to divide them into four groups:[1]

THE FOUR GROUPS OF IRREGULAR PULSES.

First, those which, either associated with certain phases of respiration or with meningitis, or in children, neurasthenics or convalescents from febrile diseases, are

1. For a more complete discussion of the cardiac arrhythmias consult:
Wenckebach, K. F.: Die Arhythmie als Ausdruck bestimmter Functionstörungen des Herzens, Leipzic, 1903.
Mackenzie, James: The Study of the Pulse and Movements of the Heart, London, 1903; New Methods of Studying Affections of the Heart, Brit. Med. Jour., 1905, i, 519, 587, 702, 759, 812.
Hirschfelder, A. D.: Graphic Methods in the Study of Cardiac Diseases, Am. Jour. Med. Sc., 1906, cxxxii, 378.
Dock, G: Recent Advances in the Study of Heart Disease, Wisconsin Med. Jour., August, 1907.
Hewlett, A. W.: The Common Cardiac Arrhythmias and their Clinical Significance, Internat. Clin., 1907, series 17, iv, 47.

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of neurogenic origin. (Fig. 1.) These are not associated with any cardiac disturbance, disappear temporarily under atropin, sometimes permanently disappear under general "tonic" treatment, hygienic measures and the administration of strychnin.

The second group, due to diminished contractility, is shown in the pulsus alternans in which, though the rate is regular, each alternate beat is small. This is most common in very rapid pulses, and as Mackenzie has shown, also in some cases of angina pectoris. It always shows that the heart is beating too fast and that its strength is insufficient, and hence if the condition con-

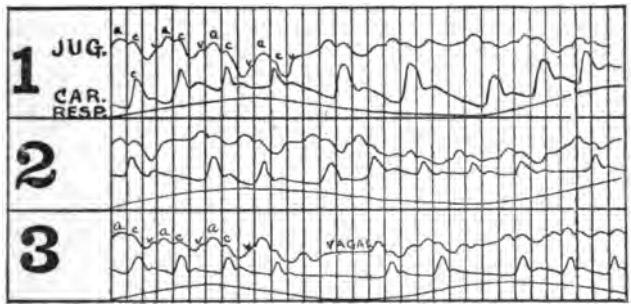

Fig. 1.—Diagrammatic. Showing the neurogenic forms of irregularity. 1. The exaggerated normal type. 2. The pulsus paradoxus. 3. Mackenzie's youthful type Upper line, pulse in jugular vein. a = wave due to auricular systole; c = wave at the beginning of ventricular systole; v = wave at end of ventricular systole. Divisions represent 1/5 second.

tinues more than a few hours it may be considered as a symptomatic indication for digitalis or strophanthin intravenously.

Thirdly, we have to deal with the three varieties of heart block (Fig. 2) at the various sites along that inverted Y-shaped path of Purkinje fibers—the sino-auricular blocks, the auriculo-ventricular blocks, and the blocks between the ventricles. Of the latter we know but little, and Doctor Hewlett[2] has told what we

2. Hewlett, A. W.: Clinical Observations on Absolutely Irregular Hearts, paper presented at this session of the Section on Practice of Medicine.

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do know. The sino-auricular block (Fig. 2, 1) as we know it, especially in the cases described by Dr. Hewlett and myself, is always functional, and since it is often brought on by digitalis it need not be added that in this digitalis is absolutely contraindicated. The same applies in the auriculo-ventricular blocks (Fig. 2, 2 and 3), whether organic as in Adams-Stokes disease, or due to myocardial weakness and vagal stimulation as in the post-influenzal or post-diphtheric conditions or due to pressure of tumors on the vagus, as in one case which I recently examined.

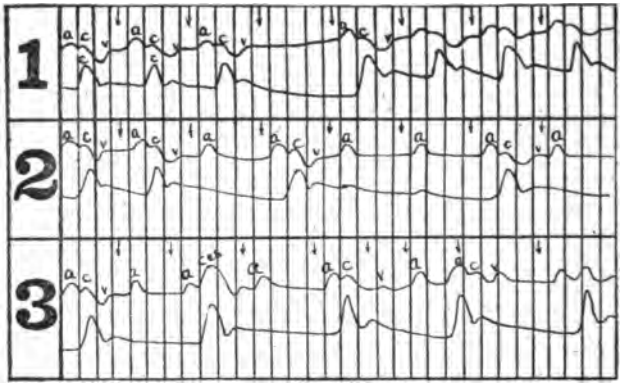

Fig. 2.—Partial and complete heart blocks. 1, sino-auricular; 2, partial auriculo-ventricular; 3, complete auriculo-ventricular block. Arrows indicated probable impulses arising at the sinus. Upper line, venous pulse in jugular vein. Lower line, carotid pulse.

Fourthly, we have the group of irregularities due to the abnormal impulses, extrasystoles, which may arise either in the auricles, the ventricles, or the bundle of His (Fig. 3). The latter group is diagnosed, I may add without absolute proof having been advanced, when the conduction time is shorter than normal. Ventricular extrasystoles are often brought about by inability of the heart to empty itself. Regularity is then restored by digitalis. At other times there is too great irritability, and in this case digitalis would only serve to increase the arrhythmia. Auricular extrasystoles may be a re-

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sult of disturbed origination of impulses, or of obstruction to the emptying of a vigorous auricle, as in mitral stenosis; as a rule they do not disappear under digitalis or atropin, but sometimes a certain amount of benefit may result from a simultaneous increase in the tone of the heart muscle.

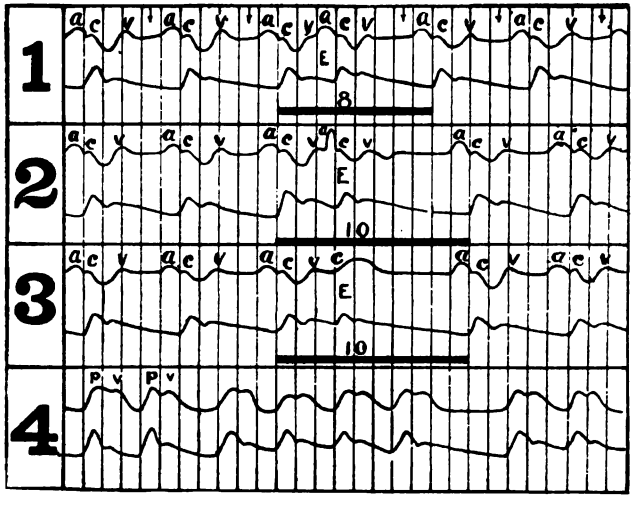

Fig. 3.—Extrasystoles, and auricular paralysis. Underlined portion indicates duration of systole + extrasystole + pause. 1, auricular extrasystole; 2, auriculoventricular extrasystole; 3, ventricular extrasystole; 4, auricular paralysis.

PAROXYSMAL TACHYCARDIA.

In paroxysmal tachycardia we also have to deal with peculiar sudden changes in rate, almost doubling and almost halving, sometimes associated with irregularity in the transitional stages but usually perfectly regular. The doubling and halving is sometimes due to the passing on and off of an auriculo-ventricular block; in one of my cases it appeared to be a sino-auricular block. I have also been able to produce it experimentally by faradizing the auricles into a state of fibrillation (Fig. 4). Under these conditions the ventricles would suddenly pass into a paroxysm of rapid rhythms, sometimes regu-

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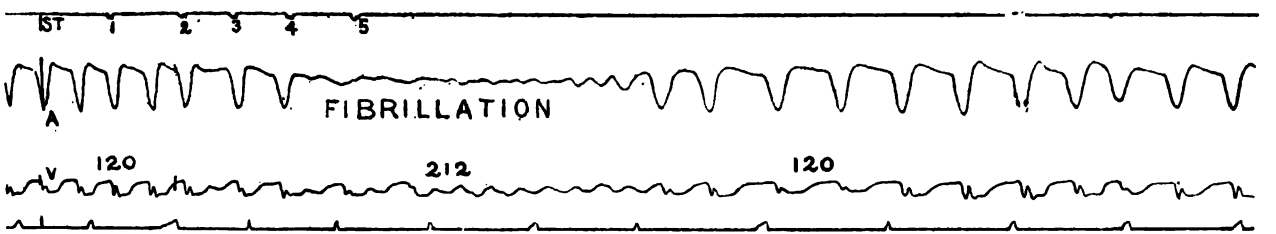

Fig. 4.—Tracing from heart of dog, showing suddenly beginning and suddenly ceasing tachycardia, brought on by faradic stimulation of the auricle A at 1, 2, 3, 4 and 5. V = ventricular contractions. Time in seconds.

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lar, sometimes slightly irregular.[3] The rhythm was then just less than double the original rate, but would rise suddenly from 120 to 213 a minute or thereabouts and drop at once to the regular rate either on vagus stimulation just as a paroxysm of tachycardia may stop; or the rapid rhythm might be resumed after the vagus stimulation had ceased and later fall spontaneously. As irritability increases, as by successive stimulation, the ease with which these paroxysms are brought on increases, as does also their duration. But even granting that this phenomenon resembles paroxysmal tachycardia, the treatment remains to be worked out further. For in that disease digitalis, strophanthus, intravenous strophanthin, strychnin, atropin, ice-bags, pressure on the vagus, and all the well-known cardiac stimulants have been known to fail, though sometimes useful.

VELOCITY OF BLOOD FLOW.

I shall now discuss the velocity of blood flow in disease. In 1904 Erlanger and Hooker[4] demonstrated that the velocity of flow per unit of time is more or less proportional to the product of pulse pressure by pulse rate. By pulse pressure is meant the variation in pressure due to the pulse beat, and hence the difference between maximal and minimal pressure. This product has no absolute value, but has a relative value as a standard for comparison in the same individual. Erlanger and Hooker found it of importance in determining the relation of blood flow to cyclic albuminuria but

3. Von Ziemmsen (Studien über die Bewegungsvorgänge am menschlichen Herzen, sowie über die mechanische und elektrische Erregbarkeit des Herzens und des Nervus Phrenicus. Deutsch. Arch. f. klin. Med., 1882, xxx, 270) produced exactly similar paroxysms of tachycardia by galvanization, but not by faradization, over the precordium of a subject in which the chest wall had been removed along with chondroma of the ribs.

4. Erlanger, J. and Hooker, D. R.: An Experimental Study of Blood Pressure and Pulse Pressure in Man. Johns Hopkins Hosp. Rep., 1904, xii, 145.

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made no observations on patients. In 1905, I followed the blood pressure in a number of heart cases over a considerable period of time, and found that in them the general condition seemed to improve when the velocity of flow (as shown by product of pulse pressure by pulse rate) increased and to become worse when it decreased, so that the patient's condition usually followed the velocity curve as shown in Figure 5.

This observation, which was unpublished, has since been confirmed by the very long and careful studies of Brun Fellner,[5] Albert Fraenkel,[6] Lust,[7] and others, who show that in general digitalis and strophanthin increase the product. This is unquestionably true, but in the case just quoted the heart muscle was too far weakened to give this response until the digitalis was combined with nitroglycerin, when the velocity was greatly increased. In many cases the change in the velocity coefficient precedes the systemic change for some time, and may therefore be of value in predicting and in warding off impending trouble, so that in many cases it may furnish a good guide for treatment, especially in bed patients.[8]

TONICITY OF THE HEART MUSCLE.

Another line of investigation which is yielding promising results is the investigation of tonicity of the heart muscle. It has long been certain that important functional changes go on in the heart without manifesting themselves either on the blood pressure or the arterial or venous pulse curve, and that these variations are the

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5. Fellner, B.: Klinische Beobachtungen über den Wert der Bestimmung der wahren Pulsgrösse (Pulsdruckmessung) bei Herz- und Nierenkranken, Deutsch. Arch. f. klin. Med., 1907, lxxxviii, 1.

6. Fraenkel, Albert, and Schwarz: Ueber intravenöse Strophanthintherapie bei Herzkranken, Arch. f. exper. Pathol. u. Pharmakol., 1907, lvii, 79.

7. Lust: Klinische Erfahrungen mit der intravenösen Strophanthintherapie, Deutsch. Arch. f. klin. Med., 1908, xcii, 252.

8. Since this article was written T. C. Janeway has published notes of a case in which the improvement bore no relation whatever to the velocity coefficient (The Use and Abuse of Digitalis. Am. Jour. Med. Sc., 1908, cxxxv, 781).

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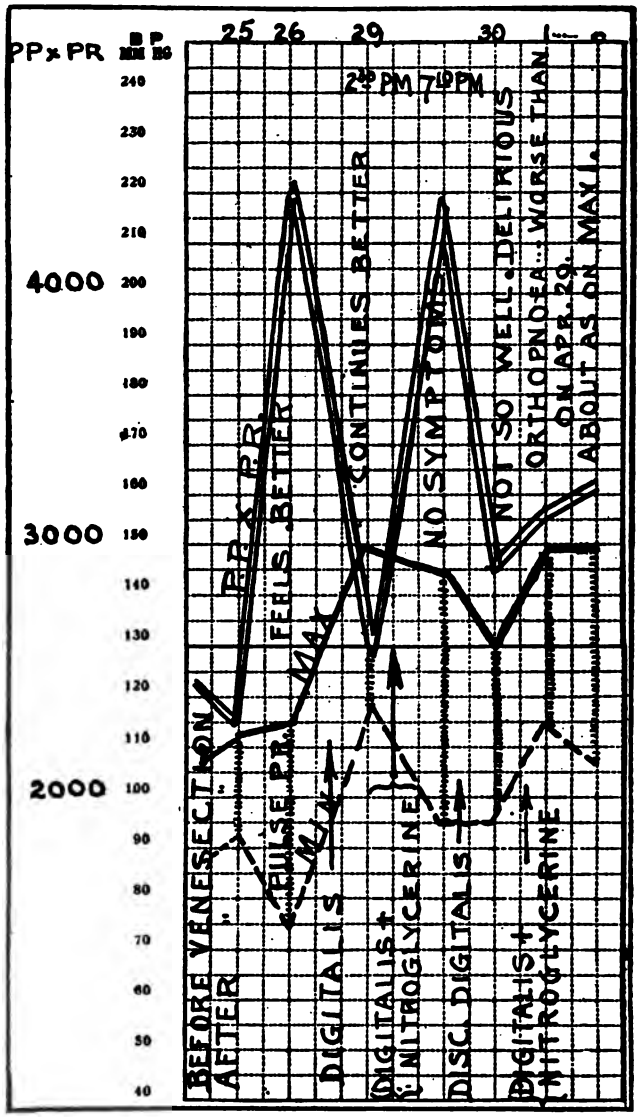

Fig. 5.—Showing course of symptoms in a case of myocarditis. = Pulse pressure × pulse rate. — Maximal pressure. - - - Minimal pressure. . . . . Pulse pressure.

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preliminary steps which determine the later changes. Many of these are due to changes in tonicity of the heart muscle. The importance of a systematic study of cardiac tonicity in mammals was emphasized by James Mackenzie in 1904, and also by Gibson and Clifford Albutt, but so far as I am aware no experimental investigation has as yet been published. The subject was therefore

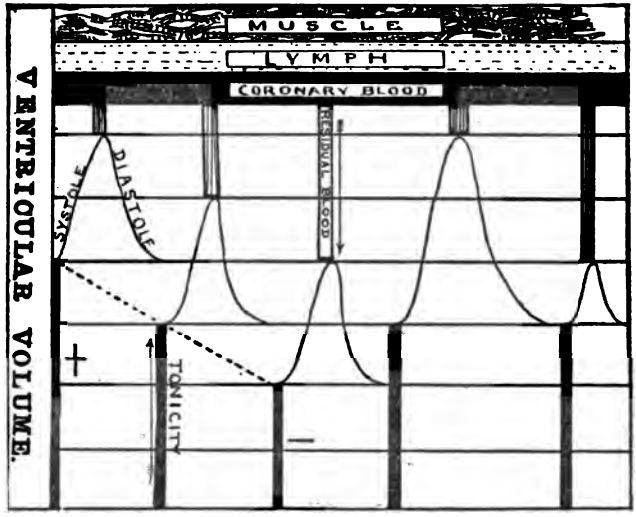

Fig. 6.—Diagram illustrating changes in tonicity and systolic output, showing elements which enter into the total volume of the ventricles and variations in tonicity with and without variations in systolic output. Length of heavy black line indicates degree of tonicity; that of shaded line amount of residual blood.

studied experimentally by Dr. Cameron at my suggestion and under my direction during the past winter. The results are now being presented as a Doctor thesis at the University of Edinburgh, and as they will be published in detail within the next few months I shall merely describe his general methods and conclusions. Tonicity may be defined as the tendency of the muscle to resist stretching or overfilling of the heart when the walls are relaxed in diastole and changes in tonicity are shown by changes in ventricular volume at the end of diastole.

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The changes in volume of the ventricles were studied by inserting the ventricles into one of Yandell Henderson's cardiac plethysmographs, so that it fitted air-tight about the auriculo-ventricular groove, and connecting this with a large recording tambour. For convenience the tambour was inverted so that upstrokes record decrease in volume, downstrokes increase. The volume at the end of diastole indicates cardiac tonicity (at least when the change of rate, etc., is allowed for), that at the end of systole shows the amount of blood residual within the ventricle. These are relative not absolute terms. The diagram (Fig. 6) shows the relation of the curve to changes in tonicity, and especially that the

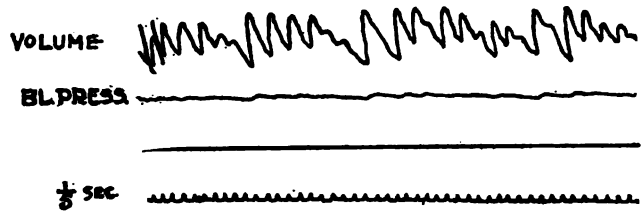

Fig 7.—Volume curve in experimental irregularity. Showing the tendency to dilatation (downstrokes).

latter is independent of systolic output. Other things being equal, an increased tonicity was accompanied by diminution in the volume of residual blood in the ventricle at the end of systole, while decreased tonicity was accompanied by accumulation of it, even to several times the amount thrown out at each systole. Such an accumulation as a rule gave rise to no irregularities nor outward manifestation other than more dilatation (Fig. 7).

Dr. Cameron found that practically all the drugs which are cardiac stimulants—digitalis, strophanthus, nitroglycerin and strychnin—increase cardiac tone to a marked degree. Adrenalin was the only one with which it was definitely diminished. The diminution in tonicity due to aconite was only about what would correspond to

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the same stimulation of the vagus. These results are especially interesting in the case of strychnin, since this effect may be obtained from doses so small that there is absolutely no effect on the mean blood pressure. Many text-books on pharmacology have stated that strychnin has no direct action on the heart, and the German writers do not include it at all in their treatment of cardiac diseases, but these studies of Cameron place the observations of American and English clinicians once more on an experimental basis.

The importance of preserving a proper degree of cardiac tone is shown also on subjecting the heart to a slight strain, as by clamping the thoracic aorta. If the tonicity of the heart muscle is good (Fig. 8, 1) there is a momentary dilatation and then the heart gradually pumps itself out and gets smaller and smaller until it is soon of even smaller volume than before the strain was put on it. Whereas, if the tonicity is low (Fig. 8, 2), the heart dilates and remains dilated; and a dilated heart works at a disadvantage, so that this may lead to further overstrain. If the heart is in very poor condition (Fig. 8, 3), the single strain may lead only to progressing dilatation and finally to death.

LABORATORY FINDINGS APPLIED IN THERAPEUTICS.

These experiments illustrate what goes on in muscular exertion and what we use in the Schott treatment. We do not give these exercises to too weakened patients, if we did it would still further depress their tonicity and make them worse. This sometimes actually happens when we are over-zealous in the treatment. But we aim to put a very mild strain on the heart, one that it readily overcomes, and one that, just as in our dog's heart, increases the tonicity and leaves the heart smaller than before, with less residual blood and in better condition to resist another strain.

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Cameron found, moreover, that the slowing of the circulation, the accumulation of CO_2 in the blood, and the slightest asphyxia caused a marked diminution in tonicity, so that in any cardiac overstrain we have instituted a vicious circle:

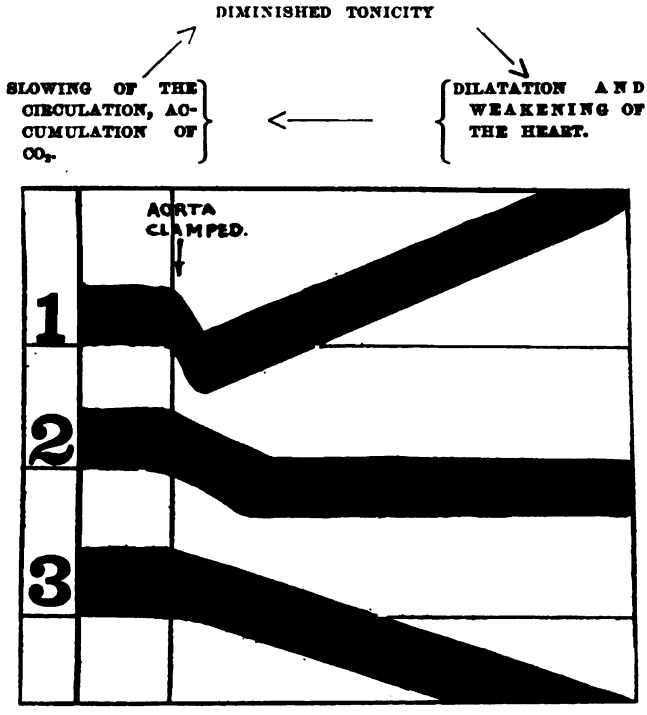

Fig. 8.—Showing effect of clamping the aorta on the volume of the heart. Diagrammatic, after experiments done with Dr. Cameron. 1, Tonicity increased by strain; 2, low tonicity, permanent dilatation; 3, very low, complete heart failure.

Another experiment has shown that the mere presence of an irregularity acts as a factor to bring about dilatation, partly by slowing the circulation and lowering tonus, partly by increasing venous pressure, so that as far as the permanent arrhythmias are concerned we have another vicious circle:

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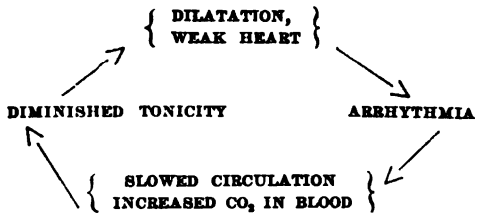

There still remain several subjects on which I should like to touch, namely, the importance of the tonicity of

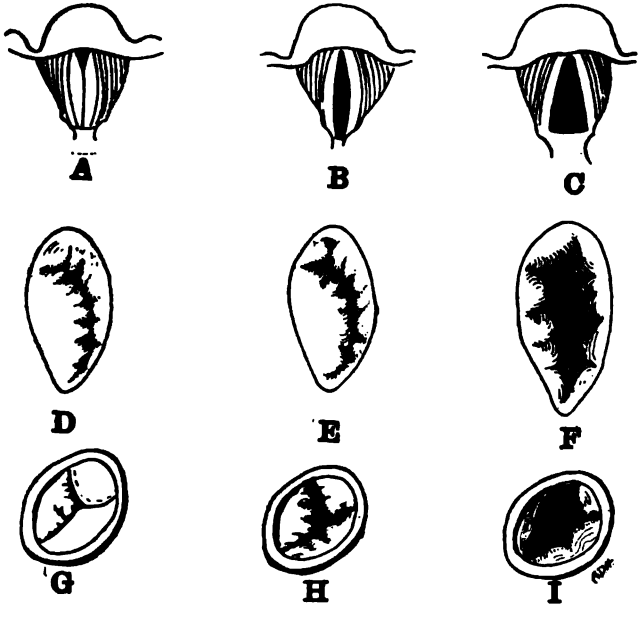

Fig. 9.—Showing analogy of positions of vocal cords for voice production and positions of heart valves in the production of murmurs. Upper line, showing larynx, with (A) vocal cords in position for high head note; (B) for low chest note; (C) for quiet breathing. Middle and lower lines showing auriculoventricular (D, E, F) and semilunar (G, H, I) valves with beats increasing from D, G to F, I.

the musculature about the mitral and tricuspid valves for the prevention of leaks, which can be demonstrated by inserting a cannula into the aorta of a sheep's heart, filling the ventricle under pressure, and observing the

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leak; throwing the muscle into heat rigor by boiling and then proving that the leak no longer appears.

RELATION OF LEAKAGE TO MURMUR.

Secondly, I should like to call attention to the importance of obtaining some idea not only of the noise made by the leak but also of the amount of leakage that actually occurs. In the experiments done with Dr. H. A. Stewart[9] on aortic insufficiency, we always found that a leak at the aortic orifice meant fall in diastolic pressure with increased pulse pressure. These leaks were sometimes almost completely plugged by fibrin, leaving only small channels for the regurgitant eddies. The murmur remained; the diastolic pressure returned to normal; and the leak was, for practical purposes, gone. As you may notice in Figure 9, the analogy with the vocal cords, a small leak with narrow orifice may give a loud murmur, while a very wide one like the vocal cords of quiet breathing may give none.

In presenting these facts and questions it has been my aim not only to present them as facts, no doubt familiar to many, but particularly with a view toward arousing or increasing interest in the experimental side, not merely of pathology and of abstract pharmacology, but of practical therapy; as a plea for the habit of carrying the problems of the bedside to the laboratory, from the patient direct to the animal, and then at once back again for verification on the patient.

DISCUSSION.

Dr. William S. Thayer, Baltimore: I wish to insist on the gravity of the pulsus alterans; these instances may last a considerable length of time, but in my experience have always been associated with grave myocardial changes. I am inclined to think that there is a tendency to-day to take rather too grave a view of the import of extra systole. I can not help feeling that a great many instances of extra systole occur

9. Stewart, H. A.: Experimental and Clinical Investigation of the Pulse and Blood Pressure Changes in Aortic Insufficiency, Arch. Int. Med., 1908, i, 102.

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in young neurotic individuals in whom one is scarcely justified in assuming the existence of serious cardiovascular changes.

Dr. G. W. McCaskey, Fort Wayne, Ind.: It is of great value to the clinician to estimate the pulse pressure by the difference between the systolic and diastolic pressure, as shown by Erlanger's apparatus. This represents the actual work done by the heart, and it indicates in a general way the working efficiency of the heart. If the systolic pressure, for example, is 200 and the diastolic pressure 175 or 180, representing a difference of 25 or 20—this being the pulse pressure—the condition is much more serious than the same systolic pressure with a diastolic pressure 35 or 40 mm. less. The pulse pressure represents the work the heart is doing. All this rests on well recognized physical laws and has its application in clinical medicine. The result gives us Erlanger's velocity coefficient, which represents still more accurately the work the heart is doing. This does not express the volume of blood the heart is forcing through the circulatory apparatus in units of any sort, but is simply an arbitrary datum available only for purposes of comparison, but certainly has a very considerable clinical value. One of the results of the work that is being done in this line to-day is the diagnostic and prognostic value obtained by the administration of drugs of the digitalis group. I have come to regard the effect of the early administration of digitalis of the highest diagnostic and prognostic value in some obscure cases of arrhythmia. If the giving of digitalis produces a bad effect on the heart I am inclined to believe that perhaps there are initial changes going on in the bundle of His which ultimately will lead to heart-block.

Dr. Arthur D. Hirschfelder, Baltimore: Extra systole is something of extreme importance. The only physical factors known at the present time to bring about extra systole are those to which I have just called attention. It is impossible to determine in an individual clinical case exactly what influences are at work. Therefore I believe that the only thing one can do under these conditions is, as Dr. McCaskey has suggested, to administer digitalis early when there seems to be a physiologic indication for it, in order to determine whether the arrhythmia is improved by it or not; in making this determination the action of the drug must be most carefully wached. It is also possible to use strophanthus in this condition if the preparation is a good one. It is a little milder and quicker in its action, but perhaps more transitory. With regard to the velocity coefficient I am sorry that I am even more conservative than Dr. McCaskey in advocating it as an index for treatment on account of the exceptions which have been mentioned. There is need of further investigations along these same lines before anything of great value can accrue from them. With regard to the value of the estima-

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tion of pulse pressure and high tension, as for example a systolic pressure of 200 and a diastolic pressure of 140, as quoted by Dr. McCaskey, I wish to call attention to the fact the pulse pressure naturally increases where there exist conditions which cause a high systolic pressure. The same amount of systolic output should give rise to greater variations in the pressure at high rather than at low pressure. Consequently one must allow for that to a certain extent. Dawson of Baltimore has approximately reached that conclusion, dividing the pulse pressure by the mean pressure. One must make allowance for and bear continually in mind those factors which produce and perpetuate high pressures.

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REMISSIONS IN PERNICIOUS ANEMIA.

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IOWA CITY, IOWA.

It almost requires an explanation for presenting any phase of a subject that has been considered so extensively in recent years as pernicious anemia, but the phenomena of remissions form a sufficiently interesting chapter in the disease to warrant its being made the theme of this brief paper.

A remission signifies but an abatement of symptoms, and so rarely does a complete restitution take place that it is to be regarded as a temporary period of improvement and not a cure. The earlier writers who coined the term progressive pernicious anemia evidently did not give due cognizance to the phenomena of remissions, because a disease process that is subject to remissions of improvement, or periods of latency, can hardly be regarded as distinctly pernicious; the term progressive is applicable in that it is not possible to bring the process to a standstill or promote a cure.

Out of a series of twenty-five cases seen during the last two and a half years I have taken a few striking instances as illustrative of remissions in pernicious anemia.

CASE 1.—*History.*—C. W., a laborer, aged 53, was admitted April 8, 1907, to the University Hospital, complaining of weakness and pain in the legs. He was a moderate user of alcohol but denied venereal infection. The family history was negative. Three years previously he had had a fainting attack after which he was confined to bed for six weeks. In December, 1906, he began to notice weakness and pain in the legs which had grown slowly worse.

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Examination.—When admitted the patient appeared very anemic and poorly nourished. The legs were weak and he was unable to stand alone. The knee jerks were diminished and there was paresthesia and a mild degree of ataxia in lower limbs. Urine examination was negative. Gastric analysis showed total acidity 35, free hydrochloric acid 10. The blood findings, with subsequent changes, are indicated in the following table:

TABLE 1.

Date.	Red cells.	White cells.	Per cent. Hb.	Poikilocytes. Macrocytes. Microcytes.	Nucleated red cells.	Polymorphonuclears. Per cent.	Lymphocytes. Per cent.	Large mononuclears. Per cent.
4- 8-07	860,000	6,400	40	++	1 normobl. 2 megalo.	64	30	6
4-10-07	945,000	4,600	20	++	.....	63	35	2
4-13-07	556,000	2,200	30	++	1 stippled. 1 megalo. 2 normobl.	61	36	3
4-21-07	710,000	2,600	35	++	.....	48	50	2
5- 2-07	1,320,000	6,800	35	mod.	.....	67	26	7
5-16-07	2.390,000	5,600	40	few.	3 normobl.	69	27	3.5
5-24-07	3,090,000	2,000	40	....	.....	65	33	2
7- 7-07	3,350,000	2,700	48	....	.....	61	33	6
8-23-07	3,580,000	9,600	45	....	.....	82	17	1
9-27-07	3,720,000	9,800	55	few.	.....	83	16	1

Treatment.—At the time of the last blood examination the patient was able to walk anywhere without support, and generally felt well. The medication consisted principally of some form of arsenic. During the first three months of his stay he tolerated the drug very well, taking as much as 15 minims of Fowler's solution three times daily. Later an intolerance was manifest and only small doses, 3 to 5 minims, could be taken. The cacodylate of sodium was substituted, but even small doses of this preparation would lead to digestive disturbances, albuminuria, and puffiness of the face, compelling a discontinuance of the medicine. Although unable to take arsenic during the last three months of his stay, the improvement in his condition steadily continued. Gastrointestinal symptoms were not present, except such as were evidently due to arsenic administration, and colonic irrigation was not a part of the treatment.

Subsequent History.—It became necessary to return the patient to the county farm in Iowa County about Oct. 1, 1907, where he continued to do well for several months, when he grew gradually worse and died in March, 1908. Unfortunately subsequent blood analyses and an autopsy examination were not obtained.

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CASE 2.—*History.*—P. J., a farmer, aged 45, admitted to the University Hospital June 22, 1907, complaining of general weakness. Patient was married, had a family of five children, was a moderate user of alcohol, but denied venereal infection. The family and medical history were negative. In the summer of 1906 he complained of weakness in the back and shortness of breath. He continued to work until April, 1907, when he contracted a cold, coughed a great deal, but had no fever or pain. Shortness of breath became so marked that he had been unable to work on account of it and because of general weakness. He had occasional nausea and vomiting but no loss in weight.

Examination.—When admitted he was very anemic, skin of a lemon-yellow tint, scleræ icteric and mucosæ very pale. A hemic murmur could be heard over the precordium. The spleen was palpable. His extremities were weak and the ankles and feet swollen. The blood findings are shown in the following table:

TABLE 2.

Date.	Red cells.	White cells.	Per cent. Hb.	Poikilocytes. Macrocytes. Microcytes.	Nucleated red cells.	Polymorphonuclears. Per cent.	Lymphocytes. Per cent.	Large mononuclears. Per cent.
6-22-07	1,470,000	860	60	++	.....	60	35	5
6-24-07	1,730,000	1,600	45	++	.....	62	34	4
6-27-07	1,430,000	2,000	.40	++	1 normobl.	64	33	3
7- 5-07	1,910,000	2,400	50	polychromasia +	.....	66	29	5
7- 8-07	2,110,000	4,200	40	mod.	.....	67	28	6
9-27-07	3,190,000	3,400	60	mod.	.....	68	26	5
10- 2-07	4,050,000	4,600	65	few.	.....	68	28	4

Treatment.—During the three weeks' stay in the hospital he apparently improved. He returned to his home to be under the care of his family physician, Dr. H. A. Powers of Emmetsburg, Iowa, who lived nine miles from his home, so that he was only able to see him about once every week or ten days. The medication was confined to Fowler's solution, but he was never able to tolerate a larger dose than 10 minims three times daily. He gradually improved, and when he returned the latter part of September, 1907, to the hospital for a second examination, his general appearance was in keeping with the improvement shown by the blood examination at this time. He appeared well and claimed to be able to do full farm work without becoming tired, and aside from an occasional swelling of the feet in the evening he suffered no discomfort.

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Subsequent History.—After returning home the patient continued well during the winter, but since March, 1908, he has gradually lost strength and is now confined to his house and unable to carry on any kind of work. I am indebted to his present attendant, Dr. Baldwin of Ruthven, for some carefully prepared slides of his blood, and from these I have estimated that a marked deterioration has taken place in his blood, since the examination last October, as poikilocytes, macrocytes and microcytes are numerous, and normoblasts are present to an extent of 0.6 per cent.

Although the serial blood analyses are incomplete, it seems appropriate to refer to a third case.

CASE 3.—*History.*—W. J. W., a retired farmer, aged 64, was admitted to the University Hospital April 3, 1906, complaining of general muscular weakness and shortness of breath. The patient did not use alcohol and denied venereal infection. The family and medical history were negative. About ten months preceding entrance he began to lose strength, and experienced shortness of breath on exertion, which gradually became more marked.

Examination.—Physical examination revealed a marked pallor of skin and mucus membranes. The spleen was not enlarged but the extremities were very weak and the muscles soft and diminished in size. He was unable to walk without support. Reflexes and sensation were normal. The condition of the blood is indicated in the following table:

TABLE 3.

Date.	Red cells.	White cells.	Per cent. Hb.	Poikilocytes. Macrocytes. Microcytes.	Nucleated red cells.	Polymorphonuclears. Per cent.	Lymphocytes. Per cent.	Large mononuclears. Per cent.
4- 3-06	690,000	4,800	30	mod.	1 normobl.	46	52	1.6
4- 8-06	600,000	4,000	20	mod.	1 normobl.	42	56	2.0
4-13-06	520,000	4,800	12	mod.	.....	44	54	2.0
4-18-06	600,000	3,900	25	mod.	1 normobl.	39	59	2.0
5- 2-06	580,000	5,900	11	mod.	.....	39.2	59.2	0.8

The blood findings show an unusually low count during the month's stay in the hospital, the leucopenia being only of moderate degree, with a marked increase in the percentage of lymphocytes and mononuclear leucocytes, the entire blood finding being suggestive of Ehrlich's aplastic type of pernicious anemia with possible lymphoid hyperplasia of the bone-marrow.

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Treatment.—The patient did not bear arsenic well, being unable to take the smallest doses. Red bone-marrow, colonic irrigation and rest in bed, formed a part of the treatment without influencing the disease process in any way, and his condition when leaving the hospital was not improved. His home physician was an enthusiast on the therapeutic virtues of a remedy called "goat's lymph" and applied it, he claimed, with apparently good results, as the patient became strong enough to walk about the town, attended to most of his business duties and enjoyed fairly good health.

Subsequent History.—Six months later he again began to decline and died in February, 1907. During the period of temporary improvement the home physician received much praise while the former attendant was given a blessing of a different kind.

OTHER CASES IN THE SERIES.

Of the series of cases referred to in this paper one patient drifted into the care of a Christian Science "healer" and another underwent the manipulations of an osteopath — both patients having very low blood counts. In each instance the treatment was followed by a remission of improvement, a fact which permitted the healing measure applied at the time to receive all the credit of the apparent cure. A number of the further remissions were observed in other cases, occurring under a variety of conditions, but in no instance could the improvement be attributed to any one definite therapeutic measure.

In the first case mentioned the change of the patient from the county farm to the hospital, with the improved hygienic and dietary condition, was no doubt a strong factor. The second patient was treated at home where the conditions were unfavorable for frequent medical attendance. Improvement in the series occurred with and without the use of arsenic.

In several instances where fermentative changes in the intestines were a prominent symptom, high colonic irrigation with normal salt solution seemed to be connected with remissions of improvement. One case of the aplastic type, which was subsequently confirmed at au-

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topsy, resisted all measures of treatment and became progressively worse. In a baby 10 months of age, with the blood picture of pernicious anemia, improvement followed the weaning and institution of a proper milk diet.

A certain parallelism is maintained between the changes in clinical signs and blood findings, the blood condition being usually a fair index of the degree of improvement in the patient and also of the reactive changes in the hematopoietic organs, especially the bone-marrow.

Barjon and Cade and other French writers lay much stress on the value of the syndrome "leucopenie-lymphocytose" in diagnosis and prognosis. The disappearance of the leucopenia and modification of the leucocyte formula suggests improvement and lessens the gravity of the prognosis; quantitative and qualitative changes in the erythrocytes being equally indicative of improvement. While Ehrlich, Lazarus, Bloch, Stengel, Senator, Stockton, Cabot and other observers have referred to remissions as characteristic of pernicious anemia, there have been very few who have been able to bear out the enthusiastic claims of Grawitz, who has reported several instances of cures or complete restitution of the blood to its normal state.

CLINICAL AND EXPERIMENTAL PERNICIOUS ANEMIA.

Although the blood undergoes a marked improvement in the remission period, it still preserves certain abnormal features indicating that a disturbance in hemogenetic function continues to exist. In this respect the experimental pernicious anemias produced in rabbits differ from the disease occurring in the human person. In using 0.5 mg. doses of the glucosid saponin and 0.02 mg. doses of ricin (a toxalbumin from the seed of the castor-oil plant) to produce pernicious anemia in rabbits—corroborating the work of Bunting—I found in several instances not only does an animal become tol-

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erant to the toxin, especially with saponin in small doses, but if the toxic agent is discontinued the blood gradually returns to the normal and a complete restitution takes place, all of which is in keeping with the statement of Bloch that certain predisposing conditions exist in the hematopoietic structures of the human species which favor the production and persistence of pernicious anemia in man.

An analogy exists between pernicious anemia and leukemia in that both are liable to remissions of improvement, both are evidently of toxic origin and associated with changes in the bone-marrow.

At best a remission is but an apparent cure, and the practical point that suggests itself is the need of reserve in prognosis and caution in interpreting the results of various therapeutic measures—as the most promising are frequently unstable, meaning an amelioration more often than a definite cure.

That pernicious anemia is an expression of a toxemia —probably enterogenic in origin—is borne out by clinical studies and experimental demonstrations, so that care of the digestive tract is a special factor in the treatment of all cases. The recent work of Herter attributing etiologic significance to specific fermentations in the intestinal tract is very suggestive and it will be of interest to learn further about his series of cases in which the treatment consisted of the removal by colonic irrigation of the *Bacillus aërogenes capsulatus* from the intestinal tract.

While the present lack of etiologic unity prevails it is evident that the explanation of the remission phenomena and the finding of a definite curative measure are problems still to be solved.

DISCUSSION.

Dr. Charles G. Stockton, Buffalo: Flint, many years ago, pointed out that in pernicious anemia a disappearance of secretions and ferments from the stomach, and the etiology of the disease was laid to a gastric atrophy. As time went

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by all gave up Flint's idea. It is a remarkable fact that he made the observation, so long ago, of the disappearance of the gastric secretions and ferments in the majority of cases of pernicious anemia. The secretions do not disappear in all cases, as has been pointed out to-day. In the cases that I have studied, and they amount to a considerable number, after a true remission I have not found a corresponding improvement in the digestive tract. There has been an improvement in certain cases; but those cases in which there was a great improvement in the gastric secretion were never cases of achylia gastrica, but seemed to be cases on the border-line; also the anemia turned out not to be true pernicious anemia. I think that we should be somewhat guarded in our classification of pernicious anemia. Cases that were formerly called pernicious anemia we hesitate to name. On the other hand, cases formerly called secondary anemias are now classed as pernicious anemia, and to that class belong the cases reported to-day. I have known these remissions to continue over a long period of time. One of the most typical cases I know of, lasting ten years, was followed by a remission which, so far as I know, still continues. I heard from this patient one year ago; he reported himself to be in perfect health. The blood count was very low and in every way the case was quite classical. I recall another case, that of a woman, who had four or five remissions, never severe but typical. These four or five remissions covered a period of eight years. These, however, were exceptional cases. From a clinical point of view these cases appear to be cases of pernicious anemia. There are few diseases that we seem to know better than this disease and yet its real nature remains obscure. As to the remedies bringing about remissions, I believe in a course of treatment not only by arsenic and hydrochloric acid, as recommended by Dr. Dock, but by colonic lavage and hygienic measures. I have seen patients get better who did not follow this course of treatment, yet I feel confident that good is accomplished by it.

Dr. William S. Thayer, Baltimore: I have seen one case of apparent recovery from pernicious anemia; this case was very similar to the one reported by Dr. Stockton. This patient was in Dr. Osler's ward in 1890, and presented the classical picture of pernicious anemia. The lowest blood count was between 800,000 and 900,000 and the color index was high. Histologically the changes were characteristic. After three or four months' treatment the blood count rose to 5,000,000 and over, and the patient left the hospital apparently well. Five years later the man came back again with carcinoma of the stomach. The blood was then normal. The patient soon left the hospital and was lost sight of. Last year I saw a second case in which improvement progressed until the blood appeared perfectly normal. This patient entered the hospital in May,

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remained two or three months and made a remarkably rapid recovery. The blood count rose to over 5,000,000 shortly after the patient's return to his home and the entire picture of pernicious anemia disappeared. Two or three months later he was still in good condition, but in February he died.

Dr. Alfred Stengel, Philadelphia: My experience has been that the more cases I see the less certain I am in making an absolute diagnosis of pernicious anemia. During the past two or three years I have seen a series of cases in which the blood picture was that of pernicious anemia, yet they differ so in their clinical course and in other respects, that I doubt whether I have made a correct diagnosis. In many of these cases there were evidences of intestinal disturbances. In one case there was a slight but continuous bleeding from the intestinal tract; the stools were constantly tinged with blood and the loss of blood in the aggregate must have been great. In another case the stools swarmed with infusoria which I could not identify. In three cases slight hemorrhages occurred, and these were occult in the stools. In another instance there were evidences of putrefactive changes in the feces. These cases all ran a typical course. All showed a rapid improvement when given intestinal lavage with simple water and instillations of nitrate of silver. All, however, relapsed eventually. Three or four patients have since died. The blood picture in these cases was largely that of pernicious anemia, but not sufficiently so as to make, in my mind, a diagnosis absolutely certain. In some of these cases the picture presented was typically that of pernicious anemia. In several cases remissions occurred from time to time. One case under my care for a year or two at one or another hospital, has been treated at either the Pennsylvania or University Hospital during the past eight years, entering nearly every year. The patient has been under my care not less than three times. He presented a typical picture of pernicious anemia; there was no mistake in this case. With regard to the treatment, arsenic relieved many of the attacks. I have known of one case, which I reported, that has been under my care four different times in four different years with relapses. These relapses, as Mackenzie has said, running over a period of years, are not infrequent. An important point in drawing deductions is to learn to differentiate between the intense anemias, anemias especially of the pernicious types, and cases of genuine pernicious anemia; but how to draw a border line in these cases I do not know.

Dr. W. M. McCabe, Nashville: I believe that if Dr. Herter is correct in his theory that pernicious anemia is due to anaerobic bacteria in the intestinal canal, then intestinal lavage is the proper treatment. I had a patient under my care at the City Hospital, in the service of Dr. John A. Witherspoon, with a leucocyte count of 3,000, an erythrocyte count of 1,500,000.

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hemoglobin index 1.5 per cent., nucleated red cells, etc. Appendicostomy was performed and the colon was irrigated twice daily with two gallons of saline solution. Several weeks after this treatment was begun the leucocyte count was 7,000, red cells 3,200,000, hemoglobin index 0.9 per cent., and no abnormal types of cells were present. It is especially interesting to note that examination of the stomach contents showed lactic acid in large quantities and an absence of free hydrochloric acid. This would be frequently examined to see if the free hydrochloric would return. At operation the stomach was examined and found somewhat contracted. No cancer was present.

Dr. Hugo A. Freund, Detroit: As a rule I would give a good prognosis in a given case of pernicious anemia, that is, for a relative length of time. All cases that I have seen came to me with a distinct and definite picture, but there were some cases, only a small number, that showed a rapidly progressive type. These are best described as primary progressive cases. I believe that the general practitioner should give a good prognosis in all the cases he meets, but only for a relatively short length of time. The influence of treatment is only relative; experience with these cases shows that but little difference is made whatever treatment is employed, whether by arsenic, hydrochloric acid, pancreatin, goat's lymph, osteopathy, Eddyism, or what not; all have been useful at times, however. There is a time when patients have blood crises, or blood showers; this I have noticed on many occasions. It has been asserted that when these showers occur dissolution is soon to follow. In a large number of cases watched at the University Hospital at Ann Arbor death did not follow; and these blood showers occurred in a large percentage of the cases. What does it mean? Probably it is an attempt on the part of the bone marrow to regenerate. If the body is attempting to restore the normal function of the blood it seems to me this is a propitious moment for such a restoration, and the giving of arsenic at this time is usually followed by beneficial results. Some of these patients persisted in a good state of health for a long time. I recall one case under observation for eleven years; I still hear from this patient and there has been no return of the symptoms. With these showers a low blood count has been noticed; cases have been reported of a low blood count, in which there has been a decided improvement following treatment; the patients get well. Some of these are remarkable cases. In these showers there usually occurs a larger percentage of nucleated red cells per centimeter than white cells. Lymphocytosis is an interesting phase in this disease; an increasing lymphocytosis is prognostic of dissolution, far more than any other particular blood picture.

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Dr. John A. Witherspoon, Nashville: I had a patient, a man, 35 years old, who had a typical pernicious anemia so far as the symptoms and blood findings were concerned. I have always hesitated in advising appendicostomy and colonic irrigations; I have generally been able to get along without it. In this case, however, I believed it wise to give it a trial. The result was that, with a patient evidently rapidly approaching dissolution, the man gained ten pounds in weight during the last ten days, and has made a marvelous improvement. Whether this improvement will be permanent or not I do not know; but it is a remarkable fact that in this case, with the patient progressively going to the bad, and apparently with but a short time to live, I should have such an excellent result from the use of colonic irrigations of normal saline solutions given twice a day; the recovery was certainly a rapid one. The fact that this patient gained ten pounds in weight in such a short time is good evidence at least of marked improvement in his powers of digestion. I shall try to keep in touch with this patient and report further in the journals. I am prejudiced against appendicostomy.

Dr. Jesse S. Myer, St. Louis: I have a patient, a man 60 years of age, who has been under my observation for over a year. He came to St. Louis from Georgia in a state of perfect collapse. He had the most marked degree of anemia that I have ever seen. There was anasarca, dyspnea and the typical picture of the blood of pernicious anemia. The intestinal symptoms were very marked, and characterized by a severe and persistent diarrhea. Because the patient came from Georgia, where there are many cases of infection with *Anchylostoma duodenale*, and because of the marked intestinal symptoms, with traces of blood in the feces, with a blood picture of pernicious anemia, I felt justified in instituting the regular specific treatment for *A. duodenale*, even though I was not successful in demonstrating the existence of the eggs in the stools. Thymol was given in large doses and the improvement was so marked that in one month the patient was able to return to his home and resume his duties. At the end of six months, however, he reported that he was in a similar condition. His physician resorted to thymol again, but without any effect whatever and the patient died. The apparent response to treatment for infection with *A. duodenale* simply proved to be a coincident remission in the symptoms of pernicious anemia described by Dr. Bierring.

Dr. Walter L. Bierring, Iowa City: Dr. Stockton's statement that in remissions of improvement in pernicious anemia there is no return of the free hydrochloric acid in the gastric juice corresponds with that of Grawitz, who firmly believes in the possibility of a complete cure in pernicious anemia, and has reported two cases, one of five and the other of eight years' standing, in neither of which was there a return of the free hydrochloric acid in the gastric secretion, indicating that

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a complete restitution to the normal had not taken place. The view expressed by Dr. Stengel that a number of similar conditions are met in which a pernicious type of anemia prevails is very apt—as evidently such states as aplastic and metaplastic anemia, chloranemia, and severe instances of secondary anemia, are closely related, all being dependent more or less on changes in the bone marrow, resulting from toxic influences acting on this tissue and other hemopoietic structures. True pernicious anemia of the Biermer type is not as common as generally believed; in fact, it is a rather rare disease. Its greater frequency in later life supports the view that changes take place with age in the hemopoietic structures which predispose to the production of this disease.

The suggestion of appendicostomy as a therapeutic measure to facilitate the irrigation of the colon is very interesting. While colonic irrigation certainly influences toward improvement this does not mean that every case of pernicious anemia is necessarily colonic in origin. The uncertainty of our knowledge of the etiology, toxic agent and portal of entry makes it difficult to judge properly the merits of the different methods of treatment that are proposed in this disease.

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A CLINICAL METHOD FOR THE DETERMINATION OF THE SODIUM CHLORID CONTENT OF THE BLOOD AND OTHER BODY FLUIDS.

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The object of this paper is to present a practical working method for the determination of the sodium chlorid content of the blood and other body fluids, together with the results obtained by this method in a variety of disease processes. Especial interest attaches to such a study because of the questions that have been raised during the past few years relative to chlorid retention and excretion in certain acute and chronic maladies.

The amount of sodium chlorid in the blood of normal individuals is generally estimated as being about 0.5 per cent. (v. Jaksch). In the oft-published tables of C. Schmidt[1] the proportion of sodium chlorid in healthy human blood is given as 0.5546 per cent., while Biernacki[2] gives lower values and finds normal variations between 0.441 and 0.468 per cent. The discrepancy in these findings probably depends on the fact that analyses of the ash of the blood are among the most difficult in chemistry for the reason that certain substances, including chlorin, are easily volatilized if too much heat is applied. Furthermore, it is to be remembered that practically all the sodium chlorid resides in the plasma, while very little, if any, is present in the blood cor-

1. American Text-Book of Physiology, ed. 2, i, 50.
2. Untersuchungen über die chemische Blutbeschaffenheit bei pathologischen Zuständen, Ztschr. f. klin., Med., 1894, xxiv, 460.

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puscles. Hence analyses of blood obtained postmortem after more or less clotting has occurred are absolutely unreliable, and the error inherent in such a method of procedure is responsible for the bizarre findings in certain recent investigations of the blood in diseased conditions of the body, as I shall presently show.

The method of sodium chlorid determination which forms the basis of this paper is one which is applicable in the routine bedside study of the patient, and one that can be easily carried out by any one versed in the workings of the regular clinical laboratory. It is an adaptation of the well-known Salkowski-Volhard method of the quantitative estimation of the chlorids in the urine and gastric contents. There would seem to be no reason why this procedure, as a clinical method, should not apply in the case of the blood, provided that the proteid constituents be first removed so that the silver nitrate used will not combine with these to form silver albuminates. In order to rid the blood of the albumins it was decided to precipitate and oxidize these bodies by nitric acid as a preliminary step. After this the method departs in no way from the routine procedure as used in the case of the urine. The results of the first experiments gave values for sodium chlorid in agreement with those of previous investigators, and further work showed variations which are exceedingly slight in degree and well within the limits of error of any clinical method.

METHOD OF OBTAINING THE BLOOD.

The requisite amount of blood is secured from one of the larger veins at the bend of the elbow by means of an aspirating syringe. A simple form of apparatus consists of a piece of glass tubing, diameter 10 mm., with tapering ends. To one end is attached a short piece of rubber tubing connected with a large-sized hypodermic needle; to the other is attached rubber tubing with a mouthpiece such as is used with the ordinary blood-counting pipette. This latter end of the glass tube is

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made large enough to readily admit the stem of a regular 1 c.c. volumetric pipette. This apparatus is easily constructed and is similar to one described in Ewing's "Clinical Pathology of the Blood,"[3] except that the needle is not attached by a ground-glass connection.

The skin on the inner surface of the elbow is thoroughly cleaned with alcohol and sterile pledgets, and the apparatus—with the exception of the long rubber tubing—is boiled. After carefully blowing out all the contained water the needle is introduced into the vein through the skin and the blood aspirated by suction. About 2 or 3 c.c. of blood are drawn into the glass tube, the needle is withdrawn, the rubber tubing connecting the needle with the syringe is compressed, the tubing leading to the mouthpiece is disconnected from the syringe, the volumetric pipette is introduced into the syringe and 1 c.c. of blood is measured out. The whole procedure can be done carefully and rapidly before there is any tendency to clotting.

METHOD OF THE CHLORID DETERMINATION.

One cubic centimeter of blood, exactly measured as above described, is placed in 25 c.c. of nitric acid solution (concentrated nitric acid, C. P. 1 part, distilled water 3 parts). The volumetric pipette is rinsed out four or five times with distilled water and the washings added to the blood and nitric acid mixture. The color varies from reddish-brown to chocolate-brown, varying very appreciably with the hemoglobin content of the blood. The albumin bodies of the blood are at once precipitated and oxidized by the nitric acid, while the sodium chlorid content is unaffected.

To this solution are added exactly 5 c.c. tenth-normal silver nitrate solution. This is well shaken, allowed to stand ten minutes, and then put in a 50 c.c. graduated flask and the amount made up to the 50 c.c. mark with distilled water. This is then poured into a clean beaker,

3. Second edition, page 67.

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thoroughly mixed, and 25 c.c. are filtered into a graduated flask of that capacity. This filtrate, which is almost colorless, is used for the titration.

Ten drops of a saturated aqueous solution of ferric ammonium sulphate are added to the filtrate as an indicator. Into a burette, graduated in 1-20 c.c., is placed a twentieth-normal solution of ammonium sulphocyanid. Titration is then carried on until every trace of silver is precipitated, when the sulphocyanid combines with the ferric salt to form the reddish-brown ferric sulphocyanid. The end reaction is very sharp and the titration is stopped at the first tinge of color.

The calculation is very simple. The number of cubic centimeters of the sulphocyanid solution required is deducted from the volume of silver nitrate solution used (5 c.c.) and the difference, in the terms of NaCl, represents the amount of chlorid, as NaCl, in one cubic centimeter of blood. $1 \text{ c.c.} \frac{N}{10} - AgNO_3 = 0.00585$ gm. NaCl.

(The calculation requires that the number of cubic centimeters of sulphocyanid solution be multiplied by 2, as only 25 c.c. of the filtrate were used and not the entire 50 c.c., and this sum is then to be divided by 2 for the reason that 2 c.c. of twentieth-normal sulphocyanid solution is equal to 1 c.c. tenth-normal silver nitrate solution.) In my experiments I made up an approximately twentieth-normal sulphocyanid solution, and then determined the exact value of 1 c.c. of this solution in terms of silver nitrate and sodium chlorid.

In the following report of cases attempt was made to study a variety of conditions which might prove to be of interest from the possible changes of the sodium chlorid content of the blood. In each case the amount of sodium chlorid in 1 c.c. of blood was determined, but for comparison with previous results in which a weighed quantity of blood was used, the sodium chlorid in 1 gram of blood is estimated by dividing the amount in 1 c.c. by

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1.060, the specific gravity of normal blood. This introduces a slight error in the cases of anemia in which the specific gravity is necessarily lower than normal.

That this method is not at all difficult to carry out, with due regard to the accuracy required in any quantitative chemical analysis, is seen in the fact that this small series of cases represents every consecutive experiment I have made with the exception of two early ones in which the technic of obtaining the blood was at fault.

REPORT OF CASES.

CASE 1.—Male, aged 43, with aortic insufficiency, broken compensation, dyspnea, cough, enlarged liver, edema of ankles; 1 c.c. blood contains 5.49 mg. sodium chlorid, or 0.518 per cent. sodium chlorid by weight.

CASE 2.—Male, aged 29, with gastric neurosis with absence of free HCl after test breakfasts. For past ten days he has been taking 3 drams of dilute hydrochloric acid daily; 1 c.c. blood contains 5.34 mg. sodium chlorid, or 0.504 per cent. sodium chlorid by weight.

CASE 3.—Male, aged 24, with epilepsy. Patient has been on a diet with restricted salt for past three months, and has taken no bromid during this period; 1 c.c. blood contains 5.49 mg. sodium chlorid, or 0.518 per cent. sodium chlorid by weight.

CASE 4.—Male, aged 40, with chronic interstitial nephritis. He has hypertrophied heart, relative mitral insufficiency, moderate dyspnea, blood pressure from 218 mm. to 235 mm., marked neuroretinitis, occasional vomiting, no diarrhea. The urine is increased in amount, of low specific gravity, with a good trace of albumin and a moderate number of hyaline casts. Determination of the chlorids in the urine shows an excretion of 4.37 gms. in 24 hours. Patient is receiving no medicines, is on liquid diet, and is being given a daily sweat-bath; 1 c.c. blood contains 5.19 mg. sodium chlorid, or 0.489 per cent. sodium chlorid by weight.

CASE 5.—Male, aged 19, with chronic parenchymatous nephritis. He has marked general anasarca, hydrothorax and ascites, and pronounced anemia. Urine: 1,950 c.c. in 24 hours; specific gravity, 1.018; albumin, 8 gm. per liter; many hyaline, finely and coarsely granular casts. Determination of chlorids shows an excretion of 6.16 gm. sodium chlorid in 24 hours. Left chest was aspirated and 1,900 c.c. serous fluid

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withdrawn. This contained 7.28 mg. sodium chlorid per c.c.; 1 c.c. blood contains 5.80 mg. sodium chlorid, or 0.547 per cent. sodium chlorid by weight.

CASE 6.—Male, aged 32, with acute lobar pneumonia. Seventh day of illness: He has consolidation of whole left lung, continuous fever, delirium, herpes, etc. Urine: 2,450 c.c. in 24 hours, with total chlorid excretion of 1.04 gm. sodium chlorid; 1 c.c. blood contains 5.65 mg. sodium chlorid, or 0.533 per cent. sodium chlorid by weight.

CASE 7.—Same patient as in Case 6. Eighth day of illness: Crisis occurred last night. 1 c.c. blood contains 5.49 mg. sodium chlorid, or 0.518 per cent. sodium chlorid by weight.

CASE 8.—Male, aged 53, with carcinoma of stomach, for which gastroenterostomy has been done. He has marked prostration and anemia. Hemoglobin, 35 per cent.; 1 c.c. blood contains 5.95 mg. sodium chlorid, or 0.561 per cent. sodium chlorid by weight.

CASE 9.—Female, aged 29, with marked secondary anemia due to bleeding hemorrhoids. Red blood corpuscles, 2,100,000; white blood corpuscles, 7,200; hemoglobin, 25 per cent.; 1 c.c. blood contains 6.24 mg. sodium chlorid, or 0.588 per cent. sodium chlorid by weight.

CASE 10.—Same patient as in Case 4. Uremic coma; duration, 48 hours; void urine involuntarily. This examination was made 27 days after that recorded in Case 4, and 3 days before death; 1 c.c. blood contains 5.34 mg. sodium chlorid, or 0.504 per cent. sodium chlorid by weight.

CASE 11.—Male, aged 17, with acute lobar pneumonia; consolidation of right lower lobe. Sixth day of disease. Urine: 810 c.c. in 24 hours, with total chlorid excretion of 1.92 gm. sodium chlorid; 1 c.c. blood contains 5.19 mg. sodium chlorid, or 0.489 per cent. sodium chlorid by weight.

CASE 12.—Male, aged 34, with Hodgkin's disease. Patient is in hospital for diagnosis and is receiving no medicine. Red blood corpuscles, 3,016,000; white blood corpuscles, 9,600; hemoglobin, 37 per cent.; 1 c.c. blood contains 5.80 mg. sodium chlorid, or 0.547 per cent. sodium chlorid by weight.

CASE 13.—Male, aged 18, with splenomyelogenous leukemia. On admission three weeks ago leucocyte count on three examinations showed 268,000, 220,000 and 241,000 white cells per c.mm., with typical blood picture. The spleen is exceedingly large. Since admission he has been treated with arsenic and *x*-ray applications. To-day blood count shows: Red blood corpuscles, 2,560,000; white blood corpuscles, 26,800; hemo-

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globin, 45 per cent.; 1 c.c. blood contains 6.38 mg. sodium chlorid, or 0.601 per cent. sodium chlorid by weight.

The sodium chlorid content of the blood in this series is seen to vary between 0.489 per cent. and 0.601 per cent. The former figure was obtained in two cases, one case of chronic interstitial nephritis and one of pneumonia, the latter in the patient with leukemia with secondary anemia. It is at once noted that the higher values are found in the patients with anemia, including one case each of chronic parenchymatous nephritis, Hodgkin's disease, carcinoma of stomach, secondary anemia due to bleeding hemorrhoids, and leukemia. On the other hand, the lowest values are found in those conditions which are associated with venous stasis as is well seen in one of the pneumonia cases, and in the patient with chronic interstitial nephritis with relative mitral insufficiency and dyspnea. These findings are in entire accord with the results of cryoscopic examinations of the blood in similar conditions. Thus, the extensive researches of Koranyi[4] showed that the freezing point of the blood is higher, i. e., above 0.56 degrees C., in anemias and those fevers which do not interfere with the respiration, including chlorosis, tuberculosis, typhoid and the various cachexias; while the freezing point of the blood is lower than 0.56 degrees C. in all diseases which are accompanied by deficient respiration or kidney function, or both, including pneumonia, broken compensation in cardiac disease, and nephritis.

In spite of the fact that the salt content of the blood is generally accepted to be practically constant in both health and disease, as is abundantly confirmed by cryoscopic studies, yet a review of the recent literature on the subject of chlorid retention reveals frequent reference to "chloridemia."

Furthermore, several monographs, representing arduous chemical investigations, have lately appeared in which the authors have found marked variations in the

4. Ztschr. f. klin. Med., 1897, xxxiii, 1-54; 1898, xxxiv, 1-52.

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sodium chlorid content of the blood in the different conditions studied. The most extensively quoted of these is a paper by Rumpf[5] who made complete analyses of the blood, kidney, heart, liver and spleen postmortem. In fifteen cases of nephritis he obtained values for sodium chlorid in the blood from 0.532 per cent. to 0.141 per cent. He concludes, in part, as follows: "In many cases of nephritis the chlorid content of the blood and of the tissues is increased; nevertheless, the chlorid content in nephritis gives by no means the highest values. Furthermore, there are cases of chronic nephritis in which the chlorid content of the blood is rather diminished than increased in spite of edema, albuminuric retinitis, and uremic phenomena."

This author's conclusions are based on results that are entirely inaccurate for the reason that the blood was obtained at the postmortem table at varying periods after death. As is well known, nearly all the sodium chlorid resides in the plasma, and the clotting and sedimentation of the blood prevented him from obtaining the due proportion of corpuscles and plasma in the specimens weighed out for chemical investigation. It was the frequent reference to Rumpf's paper that led me to devise the method of sodium chlorid determination herein contained. The results in my cases, however, are in entire accordance with the findings of cryoscopy and the generally accepted fact that the sodium chlorid content of the blood, or rather plasma, is remarkably constant both in health and in disease.

The application of this method to the study of transudates and inflammatory exudates may prove to be of interest. I have had the opportunity of making only three experiments in this direction, as follows: Arthritis of knee, clinical diagnosis tuberculosis, 1 c.c. fluid contained 6.38 mg. sodium chlorid; hydrothorax in a case of chronic parenchymatous nephritis, 1 c.c. fluid con-

5. Ueber chemische Befunde bei Nephritis, München. med. Wchnschr., 1905, lii, No. 9, p. 393.

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tained 7.28 mg. sodium chlorid pleurisy, with effusion, 1 c.c. fluid contained 6.38 mg. sodium chlorid.

SUMMARY.

The sodium chlorid content of the blood and body fluids may be accurately estimated by an adaptation of Volhard's method of quantitative chlorid determination after first precipitating and oxidizing the albumin bodies by nitric acid. The method requires one cubic centimeter of blood, aspirated from a vein, and accurately measured in a volumetric pipette. Clinical applications of this method show a practically constant value for sodium chlorid in a variety of conditions such as nephritis with and without edema, uremia, pneumonia, epilepsy, gastric anacidity, and conditions of cachexia. Variations in the amount of sodium chlorid depend on the relative proportion of plasma and corpuscular elements in the specimen examined, with the highest values in cases of anemia and the lowest figures in patients with venous stasis due to heart, kidney or lung affections.

CONCLUSIONS.

1. The proportion of sodium chlorid in the plasma of the blood is constant in conditions of health and disease.
2. The term "chloridemia" is unjustified.

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PELLAGRA.

ITS OCCURRENCE IN THIS COUNTRY; REPORT OF CASES.

R. HARLLEE BELLAMY, M.D.
WILMINGTON, N. C.

Pellagra is a trophoneurotic disease, affecting the cerebrospinal, digestive and cutaneous systems and characterized by an erythema. The immediate cause of pellagra is a fatty oil or extractive, called by Lombroso pellagrozein, that develops in fermenting and decomposing maize. This extractive is probably formed under the influence of a fungus. Poverty and unhygienic surroundings are predisposing causes, and most cases probably occur among the agricultural class, because they raise maize and eat it as a regular daily diet. Women are more often attacked than men, and children less often than adults. The disease occurs more often in patients between the ages of 30 and 50. As the erythema selects those portions of the body exposed to the sun's rays, it is more than probable that exposure to the sun is a factor in its development.

Belmondo believes that the disease is due to a specific organism. Lombroso experimentally produced in men and animals, with an extract from decomposed maize symptoms, analogous to those of pellagra. In Egypt pellagra occurs only where corn is eaten.

After a careful inquiry among farmers in regard to corn, I found the following facts:

1. Corn that is allowed to mature on the cob does not ferment or decompose after being gathered, and is suitable, as food, both for men and animals.

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2. Corn gathered before maturing on the cob always ferments and decomposes. This process of fermentation is called "heating," and that of decomposition "rotting."

3. If this decomposed and fermented corn is fed to animals (except swine), it produces a condition called "blind staggers," which is accompanied by a severe diarrhea and inability of the animal to stand. It staggers from side to side, and is apparently blind. This disease is very fatal, 98 per cent. of the animals attacked dying, and if the animal passes through the acute attack, it is spastic and never able to work again, because of stiffness of the limbs. That the acute attack is analogous to acute pellagra, and the chronic condition to chronic pellagra, is probable.

4. Farmers have learned never to give decomposed corn to their stock. When visiting other people, some farmers will not eat bread or grits, for fear of it being made from decomposed corn.

5. The extreme end of the cob, which often projects from the end of the shuck, always decomposes, and farmers cut this off before throwing it into the bin.

6. When corn is planted, the farmers watch the hills, and if any fail to grow, they are replanted. In this way, when harvest time arrives, there is some corn not mature, and if it is used in this condition there is danger of the other corn becoming contaminated by it. The better class of farmers eliminate this corn, or leave it until it matures. In spite of this, some decomposed meal is marketed. When mixed with good meal, it is scarcely noticeable, and is sold at reduced prices to the very poorest. In this way, we account for the occurrence of pellagra.

Prior to 1907 pellagra was not recognized as occurring in the United States. During that year, Dr. G. H. Searcy[1] reported eighty-eight cases of acute pellagra

1. Searcy, George H.: Epidemic of Acute Pellagra, THE JOURNAL A. M. A., July 6, 1907; xlix, 37.

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occurring at the asylum for the (colored) insane at Mount Vernon, Ala. This epidemic was very fatal, 64 per cent. of the patients dying. The maize eaten at this institution was found to be decomposed and unfit for food.

A sporadic case was reported by Dr. T. C. Merrill[2] of Colorado, Texas, in September, 1907.

Dr. J. W. Babcock, of Columbia, S. C., reported to the State Board of Health nine cases of pellagra. Three of these cases were complicated by hookworms, and treatment for this condition helped them.

Besides the cases which I report, a half-dozen more have occurred in my community. That this disease has been occurring there for many years there is little doubt, as a careful inquiry among older physicians brings to light many unrecognized cases.

PATHOLOGY.

There is fatty degeneration of the liver, kidneys, spleen, and myocardium; atrophy of the muscular coat of the intestines, and sometimes ulceration; atrophy, sclerosis and pigmentation of the skin; pigmentary degeneration of the cells of the brain, cord, liver, spleen, kidneys and heart; sclerosis of the crossed pyramidal tract in the dorsal portion; and degeneration of the column of Goll, in the median portion.

The posterior roots usually escape. Lombroso found Burdach's column and the posterior roots sometimes affected. There is, generally, involvement of the membranes of the brain and cord, with much thickening. The abdominal viscera are usually atrophied.

SYMPTOMS.

Chronic Form.—The symptoms begin in spring, with lassitude, headache, and anorexia. The epigastrium is usually tense, and there may be nausea and vomiting. Diarrhea—serous in quality—soon follows. This may

2. Merrill, T. C.: Sporadic Case Diagnosed as Pellagra, THE JOURNAL A. M. A., Sept. 14, 1907, xlix, 940.

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be very severe, numbering ten to forty stools a day. The tongue is inflamed, red and smooth. In ten days to two weeks, as a rule, there develops an erythema, confined to those portions of the body exposed to the sun. The parts most usually affected are the backs of the hands; next, the backs of the hands and forearms, elbows, face and neck, in the order named. Those who go barefooted usually have the erythema on the backs of the feet. The back and chest may be affected, but this is rare. Sandwith's Egyptian cases showed the elbows and forearms often involved. The erythema is usually bright red in color, very like sunburn, and disappears on pressure, unless hemorrhagic. There are often vesicles and bullæ, but there is little itching and burning compared to the extent of the process. Generally, in two weeks from the beginning, the erythema subsides, becoming brown in the center, and desquamation takes place, leaving a thickened, rough and brownish skin. After repeated attacks, the skin becomes sclerosed and pigmented and finally atrophies.

Application of salves and washes to the erythema does not benefit it. It seems to run a regular course, and if left alone, disappears earlier than if treated. The diarrhea is particularly stubborn, and will not yield. There is not the burning nor itching that is seen in other erythemas; for instance, genuine sunburn.

Toward late summer, the patient begins to improve, and may feel perfectly well during the winter, until the next spring, when a recurrence takes place, with greater or less severity.

After the third recurrence, the patient usually becomes much emaciated; diarrhea increases in severity, and melancholia, increasing to dementia, occurs. There may be edema and foul sweats. Paralysis of the third nerve and changes in the fundus oculi have been observed. There may be epileptiform convulsions, paresis of extensors, and paralysis of the bladder. The knee jerks and all reflexes are much increased early in the

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disease, but toward the end they are either diminished or abolished. There is no albuminuria as a general rule, and ankle clonus is rare. Blood changes are unimportant. The disease lasts five years, on an average, but may be prolonged fifteen years.

Acute Form.—This begins with pain in the epigastrium, headache, nausea and vomiting. This is followed by a severe diarrhea and stomatitis. The stools are often bloody, and occasionally there is bleeding from the gums and tongue. The patient emaciates rapidly. The erythema follows the same course as in the chronic form. There is some elevation of temperature, but not higher, as a rule, than 102 F., usually ranging between 99 and 101 F. There is delirium and a typical typhoid course, which usually ends in death in ten days or six weeks. I have never seen a patient recover.

I have ten cases of pellagra to report; three of these are of the chronic form, and seven of the acute.

CHRONIC CASES.

CASE 1.—*Patient.*—Miss L., white, aged 45, American born, family history negative.

History.—The patient had enteric fever at 20 years of age, and malaria several times. She has never been strong, but fairly healthy as a rule. She does not use alcohol, and there is no history of syphilis. She uses snuff, moderately. During March, 1907, she had headache and some distress in the epigastrium, and vomited occasionally. This was soon followed by a severe diarrhea, which was painless, and serous in quality. She became much emaciated and very weak. In early part of April an erythema developed on the backs of hands and lower part of forearms. This was much like sunburn. Very soon a few bullæ and vesicles formed. There was very little burning or itching.

Examination.—The patient's tongue was red, smooth and painful. Her temperature was normal; pulse 100 to 120. The heart and lungs were negative; abdomen flat, and nothing abnormal on examination. The pupils were equal and reacted to light and accommodation. The reflexes were much exaggerated, and there was no ankle clonus. Urine contained neither albumin nor sugar, but an abundance of indican.

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Examination of the blood revealed a well-marked secondary anemia, no abnormal cells, and absence of leucocytosis.

Course of Disease.—The erythema persisted for three weeks; then the skin became much thickened, with a brown hue, and exfoliated, leaving a rough, thickened brown skin beneath. The diarrhea continued through the summer, during which time the patient was very weak, and became much emaciated. She was much depressed, and cried often. In October, 1907, she seemed perfectly well. In April, 1908, she had a recurrence. She is now in the country, and her symptoms are much more severe than they were in the original attack.

This patient lived on a farm with a niece. Her corn supply gave out in December, 1906. She bought corn elsewhere, and used this during the winter and spring. Her niece, who lived with her, did not eat corn in any form, but patient did so daily. An examination of this corn showed that it was unfit for food.

CASE 2.—*Patient.*—Mrs. D., widow; aged 56; American born, family history negative, except that one brother had tuberculosis.

History.—The patient was never a very strong woman, but had no sickness of note. She never usd alcohol and had no syphilitic history. She felt bad during February, 1907; was often nauseated, and had no appetite. A severe diarrhea began in March, 1907, and was accompanied by stomatitis, the tongue being especially painful. An erythema confined to the backs of the hands developed in a few days. This was like sunburn, and there were a few bullæ and vesicles. She was much emaciated, and starved herself because of diarrhea.

Examination.—The patient's temperature was 98.4, pulse 110. Heart and lungs were negative; the abdomen was flat, with some tenderness on pressure. The abdominal viscera were negative. The urine contained neither albumin nor sugar, and blood showed secondary anemia.

Course of Disease.—The erythema subsided in a month, leaving a brownish, thickened, rough skin. The patient had diarrhea continuously until September, 1907, when she improved, gained flesh, and diarrhea subsided. During the winter she seemed well, with the exception of some mental depression at times. In March, 1908, recurrence took place, but was not so severe as the original attack. The diarrhea was not so severe, but stomatitis more so, the tongue being especially inflamed, red and smooth. The erythema was confined to the backs of hands as in the original attack, and was never red. but was brown in color from the beginning. The skin exfoli-

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ated, leaving the backs of hands brown, smooth and atrophic in appearance. The patient was much depressed mentally and showed some evidence of melancholia. The reflexes were much exaggerated and there was some spasticity about her gait. There was no elevation of temperature, and the pulse was 90. Examination now showed that the abdomen was negative, and heart and lungs the same. The urine was diminished in quantity, but contained neither albumin nor sugar. There was some anemia.

This patient's chief diet was corn bread and grits, a sample of which could not be procured.

CASE 3.—*Patient.*—Mrs. W., aged 36; American born. Family history negative.

History.—The patient was always healthy, up to March, 1906. At that time she had epigastric pain, headache and nausea. This was followed by a severe diarrhea, serous in character. In April an erythema developed on the backs of hands and forearms; it looked like sunburn, and was accompanied by vesicles. The patient was sick all summer; apparently recovered in October, 1906, but relapsed in the spring of 1907, having the same symptoms as in original attack, except in a severer form. She again apparently recovered in the winter of 1907, but again relapsed in March, 1908, at which time I saw her, with Dr. T. M. Green.

Examination.—The patient was now much emaciated and had a severe diarrhea. Her tongue was red, smooth and very painful. On the backs of hands and forearms, over and below each eye, on each side of back and front of neck, there was the evidence of a subsiding erythema. This condition was also evident on the under surface of forearms and on elbows. The skin was very brown over these areas, and in some places almost black. It was rough and much thickened. Erythema appeared only on face and neck during this recurrence. The patient had dementia, preceded by much mental depression. Her reflexes were much exaggerated, and sense of pain and temperature much retarded. There was slight ankle clonus, and pupils responded sluggishly to light and accommodation. The heart and lungs were negative. The abdomen was flat, with some enlargement of the spleen. The blood was negative. The urine contained albumin and casts.

This patient died May 19, 1908.

She had eaten corn bread daily and grits occasionally; a sample could not be obtained.

Autopsy.—The liver and kidneys appeared atrophied. The spleen was slightly larger than normal. Microscopically there was fatty degeneration of liver and kidneys, and extensive de-

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generation of the posterior and lateral columns of cord. The spleen and adrenals appeared normal. The brain and different levels of cord were not examined. There was some thickening of membrane of brain and cord.

ACUTE CASES.

There were seven acute cases. Three patients were colored and four white; they ranged in age between four and forty years. They were all in apparent good health before attack. There was no history of syphilis in any; two used alcohol. One of these was a chronic alcoholic; the other used alcohol only in moderate amounts. They were all American born. They all ate corn bread and grits daily. One patient had myocardial degeneration. His urine contained albumin and casts. This condition was probably due to the alcohol which he used to excess. This patient's abdomen and lungs were normal, and his reflexes not exaggerated. An examination of the urine, heart, lungs, abdomen and reflexes of the other six showed them to be negative. The pupils of all reacted to light and accommodation. An examination of their blood showed an absence of leucocytosis, malarial parasites, and bacteria of all kinds. None had the *Ankylostomum duodenale,* or its ova, in the stools. The patients were all attacked suddenly, the first symptoms being headache, slight fever, 100 to 102 F., and some nausea. There was anorexia and some gastric distress. All had severe stomatitis, six bleeding from the gums. The tongue was red, and much inflamed in each case.

Three cases in children showed the erythema well developed on the dorsum of feet. In these cases there was much inflammatory edema of feet, with bullæ and vesicles. These children also developed erythema on the backs of hands and forearms, over each eye, and on back of neck. They went barefooted. One of the other four patients had erythema on the backs of hands and forearms, elbows and back of neck. In the other three, the erythema was confined to the backs of the hands. Erythema was symmetrical in all cases. All the patients had

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diarrhea. In four cases, it was very severe, numbering thirty to forty stools a day; in two, about fifteen stools per day; and in one, three to eight stools. In two cases, stools always contained blood in abundance, and in one case, occasionally. The diarrhea in other cases was always serous in quality.

The erythema at first could not be differentiated from sunburn, but in a few days the skin became livid and vesicles developed. The skin gradually thickened, lost its angry look, and in two or three weeks, all erythema had disappeared, leaving a brownish red and thickened skin. In those cases which lasted only ten days, these changes could not be seen.

There was delirium in six cases, and in three it was well marked, for it was necessary to hold the patients in bed forcibly. The chronic alcoholic was not delirious, and diarrhea was not severe in his case, yet the erythema and stomatitis were particularly severe.

After a few days or a week, temperature was either normal or not above 100 F. In six cases there was gradual emaciation, loss of strength and development of stupor. The patients gradually passed into the typhoid state with delirium, carphologia and finally death from toxemia.

All these patients died. Three lived six, eight and ten days, respectively. One lived three weeks, two lived a month, and one lived six weeks. Every drug thought indicated, including arsenic and specific treatment, was tried in earlier cases, but, as this treatment gave no result, the other cases were treated symptomatically. In three cases autopsy was made, except on the spinal cord and brain, and nothing abnormal found. It was impossible to examine the nervous systems. Postmortem was refused in other cases. I am sorry that I can not report the pathologic changes in these cases, but circumstances prevented it. That we have genuine pellagra in the South I am sure, and there is no doubt in my mind that the above were genuine cases of the disease.

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DISCUSSION.

DR. WILLIAM S. THAYER, Baltimore: It is important that the occurrence of this disease should be brought before the attention of the Section. It is probably true that there are many cases of pellagra among us to-day which, like uncinariasis, have escaped notice. In a paper published by Dr. J. F. Babcock of South Carolina, who is in charge of the State Asylum, a number of cases of pellagra have been described. I am inclined to think that in a few years there will be perhaps nearly as many reports of cases of pellagra as there have been of uncinariasis after the publications of Stiles.

DR. JOHN L. DAWSON, Charleston, S. C.: Undoubtedly this disease, pellagra, exists among us and is not recognized. Since the paper by Dr. Babcock several cases have appeared in the city of Charleston and surrounding country. I have seen three cases, none of which would have been diagnosed had it not been for the publication of the paper by Dr. Babcock.

DR. ALFRED MEYER, New York: Is it not proper for the state and country to take cognizance of such a disease as exists in and about Charleston, and to suggest certain measures for its effacement, such as described by Dr. Bellamy? If some authority were obtained, as by the national Food and Drugs Act, some power of controlling this disease might be had. Perhaps it is more common than supposed, and will be more commonly recognized in the future, and something should be done for its suppression. I advise drawing attention to governmental rather than to individual medical efforts for the prevention of the spread of pellagra.

DR. R. H. BELLAMY, Wilmington, N. C.: When changes take place in the corn after its gathering, it has been gathered before it was mature. The meal was obtained from the corn after the ferments had produced the condition. Many believe this disease to be due to a specific organism; but if this were so the corn and meal could not be the source of infection, for these foods are always cooked two hours, and any organisms which they might contain would be killed. We have reported these cases to the State Board of Health, and are now prepared to go before the State Board of Agriculture. We have obtained the consent of the farmers to study the disease, and the farmers have been asked to be more careful in gathering the corn. I have no doubt that there are one hundred cases occurring every year that are not recognized. I myself see from twelve to fifteen cases every year. Although the disease was not seen or at least not recognized in my part of the country before 1903, there are certainly plenty of cases there now, and generally of the acute type, that is, there are more of the acute than of the chronic form of pellagra.

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PROMINENT SYMPTOMS IN THE DIAGNOSIS OF GASTRIC AND DUODENAL ULCERS.

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ROCHESTER, MINN.

The accurate differentiation between duodenal ulcers and ulcers of the pyloric end of the stomach offers great difficulties. When a physician follows his patients from the examining room to the operating table he is forced to the conclusion that to locate a peptic ulcer is not only difficult but often impossible.

In reviewing the symptoms and diagnostic features of peptic ulcer I shall take the duodenal as the type. What holds good for duodenal ulcers, holds equally good for all ulcers situated in the pyloric end of the stomach. The chief difference arises from the degree in which the characteristic symptoms are manifest.

In this discussion I wish to emphasize but four points that seem to stand out prominently and clearly in the larger number of cases: First, the periodicity of attacks of gastric and duodenal ulcers. Second, the number of years through which these attacks and intermissions or remissions have run before surgical relief has been advised, or perhaps accepted. Third, the characteristics of pain, its great diagnostic significance and its place in differential diagnosis. Fourth, the ready control of all symptoms during the period of attack by the measures that control pain—as food, alkalies, irrigation, and vomiting.

PERIODICITY.

The periodicity of attacks is so constant and striking a feature of ulcer of the stomach and duodenum that

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one can not but have in mind this lesion when the patient complains of repeated attacks, each covering days, with an intermission of normal health of varying time. The onset of symptoms is often initiated without discoverable cause, appearing suddenly and continuing without interruption for days, weeks, or even months, each day a repetition of the former, each meal producing about the same effect; first, ease—later followed by the usual syndrome of pain, or burning distress, gas, sour eructations and vomiting of sour mouthfuls of varying quantities, all these being at their worst from two to five hours after a meal.

Following this period of attack comes an intermission of days, weeks, or months, appearing, often, as unaccountably and as suddenly as did the distressing symptoms. These attacks recur at irregular intervals for years and continue for varying periods, increasing in intensity perhaps but slowly, the intermission shortening, until finally, the patient may fail to reach at any time that complete ease of previous years. Early in the period of disturbance and often for years, the interval is one of perfect health and, after the symptoms have disappeared, the patient soon reaches his normal condition. Yet again, it may be only a partial remission; the patient never quite attains normal, or his "good days" may be only days of moderate ease. The appetite is usually good until complications have changed the character of the symptoms, at which time it becomes necessary to examine carefully into the early history in order to arrive at a logical diagnosis.

These periods of complaint with the periods of intermission, each covering days or months, are so characteristic, that, excluding other details, this one feature is often sufficient to warrant a probable diagnosis.

However, periodicity is not of itself peculiar to ulcers of the stomach and duodenum. The character of the attack must be considered carefully. Gallstone and appendiceal colics recur irregularly, often increase in

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severity as attacks multiply, may, and often do appear suddenly and without known cause. All three have one feature in common; each attack is but a part of the usual round of trouble, and the intermission is but a part of the cycle. In the latter case no more than in the former may this quiescent period be regarded as that of cure.

LENGTH OF TIME THE SYMPTOMS HAVE PERSISTED.

Scarcely less prominent than the periodicity of attacks is the number of years the illness has been manifest before surgical relief has been advised, or perhaps should be advised in many cases, for at first most of these cases are medical and the conservative surgeon does not lay bold hands on them.

However, as one's experience lengthens he is inclined to the belief that error is much oftener to be laid at the door of conservative surgery than at the door of aggressive surgery, and for this reason the sufferer too often fails to get that ready and early relief which is secured only through surgery. In a series of 258 duodenal cases, there are but few with histories of duration of less than one year, and in these the symptoms were clear and often urgent. Usually the history shows that the disease has run from 5 to 20 years and not infrequently to 30 and 45, the average being just short of 12 1/2 years. Considering the facts of the long series of years with distressing symptoms always promising increase, and as years go by, with invalidism increasing, marked or complete, it seems strange, not that so many patients are urged to seek surgical relief, but rather why surgical measures are not advised sooner, or at least as soon as complications appear which indicate that the medical border line has been passed.

In the series here mentioned, this history of repetition of attacks with intermissions or remissions, together with long years (average 12 1/2 years) of trou-

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ble has been clear cut in about 90 per cent. of the cases. This should quiet the most conservative internist who feels that surgery is too "freely and flippantly" advised.

SIGNIFICANCE OF PAIN.

Pain in gastric ulcer is the most constant symptom and perhaps the most characteristic in its manifestations. Not the kind of pain, not the location of the pain, but the time of the pain is the distinguishing feature. It varies from mild distress to that of great intensity, and, unless complications have introduced great modifications, its appearance, control and disappearance, are almost if not quite the final evidence required for a correct diagnosis. The pain appears sometime after meals; oftener it is as nearly exact to say before meals. Usually in from two to five hours after a hearty meal the burning, gnawing feeling begins, increasing in intensity until vomiting or irrigation has removed the acid-offending material. Food eases the pain, the heartier the meal the longer the relief. Especially is this true in the history of duodenal ulcer. Gradually, however, this relief lessens, until late in the history and after the patient has been long a "surgical case," food eases but little. When complications (perforations, adhesions, obstruction) are far advanced, food gives no ease and distress follows its ingestion. At this stage relief comes only after ridding the stomach of all offending material by irrigation or forced vomiting.

The pain comes, then, in definite periods of attack; comes daily, or two or three times a day, during this period; comes from two to five hours after meals and is therefore premeal as often as it is after-meal in time. It is epigastric, radiating seldom to other areas, and, except in the later stages is relieved in part, at least, by food, drink, alkalies, vomiting and irrigation. The kind of pain depends on the pathologic condition. It may be burning, gnawing, lancinating, boring—cutting (apple-core sensation) or the felling pain of perforation.

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Locating an ulcer of the peptic tract from the area of pain as given by the patient is perplexing and often very uncertain. Most of the pain is epigastric, let the lesion be where it may, but the lower the lesion, the oftener is the sensation of pain to the right of the median line, and some ulcers, especially the duodenal variety, give characteristic findings. The longer food gives comfort, other things being equal (as duration of time of disease, extent of trouble, obstruction, etc.) the farther down is the ulcer situated, so that in duodenal ulcer, especially in the early days of its history, food gives relief for a longer time than when the ulcer is located higher, i. e. in the stomach proper. Following this period of ease, the characteristic ulcer symptoms return, of gnawing, boring even to extreme pain, with gas, sour eructation, vomiting of various amounts and intensity, dependent on obstruction and extent of lesion.

There is, however, a pain of the cardia comparable to the boring of a bared apple core, very distressing, foreboding and sickening which may be present when the lesion is purely pyloric or duodenal, and is doubtless present at times when acidity is high but purely a functional disorder or due to dietetic error. This pain is brought about by reverse gastric peristalsis, acidity, ulcer, then spasm of the pylorus followed by reverse peristalsis. If the sufferer belches or vomits with difficulty the annoyance amounts to real pain, and fear of cancer is prominent. These pains come in wave periods of a few moments, and relief follows suddenly and completely at each wave if gas and sour eructation be copiously raised, or the pain gradually recedes to almost quiet, if belching, eructation or vomiting is impossible. These wave pains repeat until the stomach is relieved by measures that empty it, or they yield readily to sufficient alkalies.

It is seen, therefore, that difficulties arise, and that the most careful attempts at ulcer location fail, but un-

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til obstruction is advanced or the lesions large, the best evidence for ulcer localization is the length of time that food gives relief.

Most of the ulcers of the stomach and duodenum (and this is true independent of location) have a longer or shorter spell of relief from food, until late in the disease, at which time the early history is necessary both for diagnosis and localization of ulcer.

There are to-day clinicians who persist in the idea that if ulcer of the stomach is present, food gives immediate pain, or at any rate, no sense of comfort even for a short time. This is not true in the great majority of peptic ulcers, let the lesion be where it may.

The great number of ulcers are in the pyloric end, and in this region the symptoms are usually typical until complications arise. We then have to consider the conditions that alter the character of the pain. They are: First, large areas (saddle ulcers); second, ulcers well toward the cardia; third, cases in which obstruction is advanced; fourth, hour-glass stomach; fifth, perforation; sixth, adhesions to the gall bladder or other organs when these adhesions cause obstruction, immobility, or deformity. In many of the above conditions the patient rarely has any perfect relief, and if there is a brief period of relief it is so soon followed by greatly exaggerated distress that the interval of ease is lost to most of them.

CONTROL OF SYMPTOMS.

All symptoms are usually controlled by the measures directed toward pain. When pain is at its highest, so also is gas, eructation and vomiting. By removing, neutralizing or engaging the acid in the process of digestion, the pain stops, gas no longer forms, vomiting and eructation cease and the patient enters a period of calm, to return to his former distress sometime later. The degree of discomfort depends on the extent of the lesion, the kind of food taken and the care in its

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mastication. Until complications (obstruction, perforation, adhesions) have advanced, the pain and other symptoms seem chiefly due to increased acidity and spasm. Reverse gastric peristalsis adds to the discomfort. Later, when complications enter for consideration, the real symptoms are obscured, and the physician is often obliged to grope in the dark for an exact diagnosis, unless the patient has a judicial mind and can relate accurately his earlier symptoms.

Again, the course of ulcer, like cancer, may be long latent, and be diagnosed only when some threatening symptom like perforation, suddenly prostrates the patient. If the perforation is not complete, or if only a small amount of septic material escapes, the pain may be of short duration, but intensely sharp and lancinating, simulating so closely gallstone colic that such diagnosis is the only logical one to make. If the perforation is free and the fluid septic or large in amount, the pain is much more intense than in gallstone colic. There is exceeding great shock, much morphin is required to control the symptoms, and early the appendiceal region will be the center of the pain. Later, if the patient survives, the pain will creep to the duodenum and gall-bladder area. Under such conditions one should think of perforating ulcer rather than gallstones or appendicitis.

When, therefore, there are attacks of stomach trouble that run in continuous periods of days or months, with intermissions of days, weeks, or months with more or less freedom from symptoms, these periods recurring and occurring over years of time gradually deepening, the symptoms bearing close relation to food and being controlled or modified greatly by dietetic measures, food, drink and alkalies, we may justly look for ulcer of the stomach or duodenum in a large number of cases.

Purely functional hyperacidity may give symptoms difficult or impossible to differentiate from early ulcer.

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Appendicitis and more often cholecystitis may run a train of symptoms that will mislead the most painstaking clinician, but these cases are as purely surgical as are typical ulcer cases. Comprehensive surgery finds the source of the trouble and relief is the result. If a mistake is made it should be that of diagnosis only.

DISCUSSION.

Dr. William J. Mayo, Rochester, Minn.: Acute ulcer is not of itself a surgical condition. It is only when such complications as perforation, hemorrhage, or obstruction occur that the physician should call the surgeon. In regard to chronic ulcerations, while the improvement between the attacks, which may last for days, weeks, months and even sometimes for years, is not by any means complete, it is sufficient to give the internist a wrong idea in regard to the cure of the patient, just as in the early days of appendicitis or gallstone disease. The surgeon considers chronic ulcers only those ulcers with thick callus which can be demonstrated to the bystander within a distance of six or eight feet from the operating table. As a result of operations it has been shown that chronic ulcers are more frequent in the duodenum than in the stomach, and that at least two patients out of three operated on are males. I do not believe that a large percentage of these patients with chronic ulceration will recover permanently under medical treatment. The preoperative stage depends largely on the length of time the patients are able to get along on a reduced selected diet; but among the laboring people one must face the conditions as they exist. The patient must not be cared for medically too long and made to live on insufficient food and ill-prepared food, such as his situation in life affords. Such a patient is disabled when living on a restricted diet, and can be restored to his full capacity for work only by enabling him to live on what he is able to pay for, and to do this operation is often necessary. In 187 resections for cancer of the stomach 54 per cent. of the cancers originated in ulcers. This does not mean, however, that most ulcers undergo cancerous degeneration. Cases with a long history of ulceration more often result in obstruction on the development of cancer than primary malignant disease of the same stage, and it is this early obstruction and not the cancer itself which sends the patient to the surgeon. Chronic ulcer existing over a period of years is, however, a grave menace to the patient because of the possibility of malignant disease grafting on ulcer base. Many people suffer severely from symptoms that may point to ulcer for which they have received no relief; these patients pass from one physician to another, to quacks and "patent-medicine" vendors. In a

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number of such cases one-half will be non-surgical and can be placed in three groups, namely, cases of atonic dilatation, cases of prolapse of the stomach and cases of gastric neurosis. In examining cases of atonic dilatation on the operating table one finds no obstruction and the wall of the stomach is quite flaccid. Apparently it has not sufficient power to push on the food. Atonic dilatations are not often benefited by surgery. In cases of prolapse of the stomach the x-ray plates look like works of art when bismuth is used to map the organ out. Such a prolapsed stomach, however, empties itself quickly; there are no mechanical conditions actually present. I do not know the definition of gastric neurosis. Some of those cases called neurotic years ago have since been relieved of gallstones, appendicitis, etc., and in the future more will be relieved. This "I do not know" group is a large one. The picture is that of a patient with gas, changing secretions, dyspepsia, indigestion, and the stomach will be found thin-walled, dilated, and the duodenum and pylorus dilated as well. It is said that many of these cases are due to pressure of the superior mesenteric vessels on the third portion of the duodenum; but this has not been found true on exploration; as a rule the jejunum and transverse colon are also dilated. At any rate they should not be subjected to operation. In the above series, one-half of all the stomach cases that come to us can be placed.

The remaining one-half of apparently serious gastric diseases belong to the surgeon. One-fifth are cases of gastric cancer; the internist has no business with them. One-fifth are cases of chronic ulcer, and the majority of these belong to the surgeon. Two-fifths are made up of a peculiar and most interesting group of cases in which ulcer has been suspected, but could not be demonstrated on exploration. Gastroenterostomy has occasionally been done and found to be harmful. Later these patients have been found to be suffering from gallstones or an inflamed appendix, tuberculosis or tumor of the intestines, etc., giving rise to the stomach trouble. The embryology of the intestinal tract explains this; the maintenance of the body is a primitive function which existed before the development of the nervous system. The cerebrospinal system does not control the primitive function, which is still cared for by the internal secretions, etc., which cared for it before the nervous system developed. The acid in the pyloric end of the stomach controls the output from the stomach. The acidity in the duodenum is the more powerful and controls the opening and closing of the pylorus. The stomach in the storage end is a later evolution and a convenience, enabling its possessor to place rapidly a quantity of food into this receptacle for the slower process of digestion, but its control is vested in the parts to be convenienced lying beyond the pylorus, which have the work to do, all derivatives of the midgut. Therefore the control of the pyloric apparatus lies

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not in the stomach itself, not in the cerebrospinal system, but in the intestinal tract lying beyond the pylorus and between it and the splenic flexure of the colon, which marks the beginning of the primitive hindgut. Therefore, gallstone disease, appendicitis, tumor and disease of the intestinal tract cause closure of the pylorus, and symptoms referable to the stomach arise which in our ignorance we have hitherto treated as diseases of the stomach. The cases comprised in the remaining fifth are surgical, but not fully worked out.

Dr. Fenton B. Turck, Chicago: In carrying out experimental research on dogs I have found it necessary to see the opened abdomen and the evidences of ulcer in order that I might know that the feces used in investigation were actually from an ulcer case. Therefore, the observations of the findings, in connection with the symptoms in these cases, have given me some idea of the existing relations and I have not yet found that the clinical symptomatology of the patient helps a great deal in diagnosis. I have seen a great many cases of ulcer of the stomach without any symptoms of pain whatsoever; I have seen cases of hypoacidity and cases of total absence of hydrochloric acid (achylia gastrica). Likewise in experimental animals with induced ulcer more frequently no evidence of pain can be elicited by pressure and there is frequently no increase of acid in the stomach—often a greatly diminished amount. In the patient the feces many times show no evidence of hemorrhage, no occult blood. These conditions I have found paralleled in the dog.

The general or systemic condition of the patient permitting ulceration to take place has not been presented sufficiently. I think that the emphasis placed on a local condition does not represent the true pathology of ulcer. Ulcer of the stomach is not found in those countries where the inhabitants eat rice. It is evidently a meat-eater's disease; the zone of ulcer is in the meat-eater's zone. Ulcer is not found among the natives of China, Japan or India, except in the seaports, which the foreigners have brought into the meat-eater's zone. Certain observations which I made with extract of meat and the colon bacillus to determine the etiology of ulcer were tabulated over a period of ten years. The attempts made on the local mucosa to produce ulcer were negative, while those made in the feeding experiments were positive. I was able to induce numerous ulcers in the duodenum at a point just beyond the pyloric region, and also in the stomach, with perforation and chronic ulceration. The question is, How does the ulcer become chronic? In the production of the acute ulcer I found the autolysis to be continuous and at times anaphylaxis, with no round-cell infiltration (chemotaxis); but in the making of the chronic form, by carefully adjusting the feeding experiments so as to bring about an alternate mild anaphylaxis and chemotaxis, I produced a condition resulting in the chronic ulcer.

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DR. JOHN M. ALLEN, Liberty, Mo.: In 1872 I made postmortem examinations of two patients, male and female, who died from peritonitis, the result of perforating ulcers in the duodenum. These were typical cases of the so-called dyspepsia. The postmortem made a deep impression on my mind; henceforward I carefully examined every case of dyspepsia that fell under my observation either in my private or clinic practice—the clinic practice began in 1881 at the University Medical College at Kansas City, Mo.—until, I think, I well established the clinical symptoms of chronic inflammation and ulceration of the duodenum which, to my mind, explained many cases of the so-called dyspepsia, catarrh of the stomach and so-called stomach diseases, not including the neurotic functional diseases of the stomach. I made a careful study of organic diseases of the stomach, particularly that of ulcer. I found eighty-six cases of chronic inflammation and ulceration of the duodenum and one case only of ulceration of the stomach. The number of patients examined was over five thousand. In 1878 I read a paper before the Clay County (Missouri) Medical Association on the subject of ulceration of the duodenum as compared with ulceration of the stomach. In 1884 I published an article on this subject in the *Aesculapian*, Kansas City, Mo.

The above statement is made as a basis for my objections to some points in Dr. Graham's paper. The symptomatology, etiology and pathology of ulcer of the stomach and ulcer of the duodenum differ widely. 1. Symptomatology: Pain is a prominent symptom in ulceration of the stomach, but not in the ulceration of the duodenum. Hemorrhage is a diagnostic symptom in ulceration of the stomach, but not in ulcer of the duodenum, in which it rarely occurs. While both are accompanied by progressive emaciation, this symptom is far more pronounced in duodenal ulcer because of the function of the duodenum. I have not observed the periodicity or remissions referred to by Dr. Graham in either of the diseases. The changes in symptomatology have always appeared to me to be the result of errors in diet. 2. Etiology: Ulcer of the stomach is the result of embolism, thrombus or arteriosclerosis of branches of the gastric artery. In thirty-eight cases of acute gastritis, some of which involved the submucous membrane, I did not see a single case of ulcer following, whereas ulcer of the duodenum results from extensive burns, acute inflammation of the organ, any of the neuroses of the stomach attended with hyperacidity, the extension of inflammation from any of the mucous inflammations of the alimentary tract, dysentery, typhoid fever, etc. 3. Pathology: There is not much difference in the character of the ulcers in each organ, but wide difference in the number of ulcers. There is rarely more than one ulcer in the stomach, whereas from three to six or eight may occur in the duodenum. While it is true that post-

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mortem investigation demonstrates that ulcer of the stomach may heal, yet the danger of perforation is so great that it is imperative to resort to surgery as soon as a diagnosis is made. I have no faith in internal medicines as a curative agent in ulcer of the stomach. In cases of duodenal ulcer, internal medicine can do great good, provided we control the physiologic function by giving only food that the stomach can digest and assimilate and administer intestinal germicides and remedies to control the reflex irritation of which the duodenum is the abdominal center.

Accepting the theory that intestinal ulcers may change to cancerous structures which, in my observation, occurs more often in the duodenum than in the stomach, I hope to hear Dr. Mayo soon announce the point at which internal medicine in the treating of chronic inflammation and ulceration of the duodenum shall be superseded by exact surgery. I have one case under observation in which jejunostomy was performed successfully in a case of ulceration of the duodenum.

Dr. Bertram W. Sippy, Chicago: There is an apparent disparity in the statistics of Robitanski, Mayo, Moynihan and others, in regard to the relative frequency of ulcer of the duodenum. I believe that the disparity can be explained thus: Duodenal ulcer is relatively more severe than gastric. The danger of perforation and hemorrhage is greater and the symptoms are more striking and more severe; as a result these cases appear before the surgeon more frequently than do the cases of gastric ulcer, which heals under treatment, or under no treatment. The cases reported by these men include those described as fresh ulcers. It is possible that ulcers in the duodenum might be overlooked; but it is not necessary to assume that all are overlooked. The disparity between the statistics of the surgeons to-day is attributable to the fact that the duodenum is more in the domain of surgery than is the stomach.

In a given case the following should be considered: Is an ulcer present? What complications are present? Is it possible that there is malignant disease at the pylorus? Is there obstruction at the pylorus? Are there perigastric adhesions? Is the pylorus open? Is the gastric secretion present? Is the motility of the stomach interfered with? All these points should be determined in a given case. Then the possible location of the ulcer should be made out. An old ulcer would be indurated. After a careful analysis one should be able to make a diagnosis of the presence or absence of an ulcer and, if any complications exist, whether or not surgical treatment should be instituted. Surgery should be invoked when perforation is present, when a carcinoma is engrafted on the seat of an ulcer, or when medical means have failed to cure. When the motility of the stomach is disturbed by perigastric adhesions or by the hour-glass constriction, one must resort to

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operation; in certain cases of hemorrhage also. In 15 per cent. of the cases death occurs during the first hemorrhage. In 35 per cent. death occurs within twenty-four to thirty-six hours. Some patients could be saved by surgical interference. I advise against waiting.

Dr. Elliott P. Joslin, Boston: Dr. E. A. Codman recently published a paper in the Boston Medical and Surgical Journal, in which the possibility of the root of the mesentery pressing on the duodenum was discussed and considered as an etiologic factor in the production of gastric and duodenal ulcer. Dr. Codman's evidence was obtained by injections in the cadaver, observations at operation and clinical studies. In animals the mesentery hangs vertically, so that there is no obstruction. but in human beings in the erect position the mesentery hangs along the spine and thus could easily compress the duodenum where it crosses it. Statistics on sex and age in gastric ulcer, I believe, should be modified. It is commonly considered that gastric ulcer occurs more frequently in women than in men, and particularly of women of the chlorotic type. During the past few years chlorosis has become a rather rare condition. Coincident with the diminution in cases of chlorosis it is a question whether there will not be a simultaneous disappearance in the disparity of the preponderance of gastric ulcer in the female sex.

Dr. G. W. McCaskey, Fort Wayne, Ind.: The point brought out by Dr. Graham as to the extreme chronicity of the disease should be recognized. I have seen in consultation a very severe case of hemorrhage which proved to come from a gastric ulcer. and in getting the history the fact was brought out that the first attack had occurred twenty-five years ago. During this interval of twenty-five years a number of attacks had occurred. Another patient seen seven or eight years ago had a distinct palpable tumor, and the question arose whether it was a cancer of a gastric ulcer. The diagnosis was made of an ulcer. The patient is alive and well to-day. I am inclined to believe that we should attach considerable value to the time of the appearance of pain in making a differential diagnosis between gastric and duodenal ulcer. When food passes from the stomach into the duodenum, then pain was supposed to occur in cases of duodenal ulcer, and I attach much diagnostic importance to this point.

Dr. Mayo, in his discussion of acute gastric ulcer, spoke of hemorrhage as being an indication for surgical interference. I understand that surgical interference in cases of acute hemorrhage is a most hopeless proposition. The great difficulty is to find the bleeding point. The best treatment, in my opinion. would be rest, and not surgical interference. Carcinomatous degeneration of the ulcer, cancer, might occur in these indurated ulcers and they should be excised whenever possible. Gastroenterostomy should not be done in these cases.

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Dr. Judson Daland, Philadelphia: In chronic ulcer, the one requiring surgical interference, we are often deceived by an apparent recovery—an important point for the internist to consider. A few months ago I had a patient under my observation who presented symptoms of ulcer, but he apparently recovered. In spite of the fact that no symptoms existed, an operation was performed and an indurated ulcer found. There are many such cases of latent ulcer that call for surgical interference. I recall another patient who died from an initial hemorrhage. This case was looked after by a skilled specialist who thought the patient was cured of his ulcer, as there were but few dyspeptic symptoms. The patient was on his way around the world when he was suddenly taken with a hemorrhage and death quickly followed. At autopsy a gastric ulcer was found. The point that I wish to emphasize is that there are many cases of chronic gastric ulcer diagnosed as acute ulcer, the symptoms appearing for a brief time only, but the ulcer remaining for years.

Dr. M. Milton Portis, Chicago: The dangers of gastroenterostomy are so great that I believe that one should hesitate a long time before advising such an operation. Two years ago I published a paper in the Annals of Surgery, in which I had collected both the medical and surgical results following a gastroenterostomy. I had been stimulated to do this because of a few cases that fell under my observation. There is no doubt at all that serious dangers follow gastroenterostomy. Jejunal ulcers occur and severe diarrheas which lead to death. There are many other disturbances. Pawlow's and Starling's work throws much light on the disturbances noted. But the strictest indications must be present before one should resort to surgical interference. In case a medical man did not want to attend the case alone, let him call in the surgeon in consultation and thus reduce the danger.

Dr. Christopher Graham, Rochester, Minn.: In differentiating between gastric and duodenal ulcer a good point is that in duodenal ulcer the food gives relief for a longer time. The degree of acidity, rather than the length of time the symptoms have been manifest, determines the severity of attack. The higher the acidity, other things equal, the greater the pain and the shorter the period of food relief.

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A CONSIDERATION OF THE COMPENSATORY DIARRHEAS.

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The literature concerning compensatory diarrhea or, as it has been more often called, vicarious diarrhea, is, contrary to expectation, extremely meager. Reports and experiments pertaining to this subject, published during the last twenty years, with few exceptions deal with but one form of compensatory diarrhea, namely the diarrheal symptom of uremia, and have added very little to our understanding of the phenomenon. Likewise, not one of a goodly number of experienced clinicians with whom I conferred on the question of compensatory diarrhea, knew a particle more than the text-book fact of the possible assumption of vicarious work by the bowels in uremia.

Compensatory diarrhea, however, may supervene in manifold conditions and at various stages of a progressive affection. In exceptional instances only will compensatory diarrhea be encountered as a terminal symptom. It is always symptomatic of arrest or perversion of the function of the skin, lungs, kidneys or the organs of internal secretion. Its immediate effect tends to systemic correction or compensation in the majority of instances and is, therefore, of a salutary nature.

As a matter of fact, most functional diarrheas have a corrective tendency, so far as the bowels themselves are concerned, but they do not call forth a general compensatory effect. Such diarrheas may diminish the in-

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tra-abdominal tension and relieve certain phenomena in a mechanical way, or they may prevent further absorption of toxic material of ectogenous or enteric origin. However, it is no vicarious function which the intestines perform by the agency of such diarrheas, and, whether we characterize them as nervous, morning, refrigatory, summer, winter, etc. diarrheas, they are nothing more than the unloading of more or less fluid intestinal contents of non-catabolic production.

Before entering on a consideration of the types of compensatory diarrhea it is necessary that the precise meaning of the term compensatory diarrhea be understood. I would define it as a phenomenon of varying degree and duration, apt to ensue and to return with more or less frequency in the course of systemic deterioration, and characterized by the diarrheal discharge of incompletely or perversely catabolized substances, or by that of catabolic products normally excreted by other emunctories.

This definition excludes, therefore, all the diarrheal eliminations of food residues and the elements elaborated from the ingesta which have not been absorbed, and includes the diarrheal excretion of normal and abnormal products of retrograde tissue metamorphosis. The evacuations in compensatory diarrhea, of course, consist, in addition to the catabolic material, of the accidental contents of the bowels. While by its nature a compensatory diarrhea is primarily always a functional occurrence, the catabolic substances excreted by it may give rise to intestinal lesions which in turn may prolong or intensify the diarrhea, or may occasion more or less severe attacks of watery evacuations of non-compensatory character. Thus, we frequently encounter in the intestines an apparent anatomic substratum of a compensatory diarrhea which, however, is but the immediate result of the perverse elimination of a number of excrementitious substances, and therefore not the

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cause but the consequence of the assumption of intestinal compensatory activity.

I recognize three general types of compensatory diarrheas, viz:

First, diarrheas which are concomitant with deficient or perverse catabolic processes.

Second, diarrheas which are the consequence of functional or structural disease of certain excretory organs.

Third, diarrheas occurring during the period of physiologic systemic decline.

The first category comprises the diarrheal phenomena which may accompany or are expressive of histolytic and histoenzymic autotoxicoses. To this belong, among others, the specific diarrheas of gout, exophthalmic goiter, Addison's disease and diabetes.

In gouty individuals, especially in those disposed to obesity, there exists as a rule a proclivity to constipation. In the so-called retrocedent and the irregular forms of the affection the paroxysms are often preceded by more or less fecal retention. Now, it is not uncommon that such a paroxysm be aborted, or that even serious interval complications be prevented, if rapid elimination of the offending material takes place by a succession of free bowel discharges. There is no doubt that the permeability of the kidneys is often interfered with in the chronic gouty state—be it on account of a cirrhotic condition of the renal structures or the clogging of the uriniferous tubules with deposits of urates or alloxur bases—and that the eliminative efforts on the part of the system may evince themselves by enforced intestinal activity. Although the urine contains at such times the usual or even an increased amount of alloxur bases, these, nevertheless, occur in the diarrheal feces in appreciably larger than normal quantities.

Since the nucleins, the mother substances of the alloxur bases, when exhibited in the fecal matters are to the greater part body-nucleins, as has been shown by

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Weintraud,[1] the connection between the abortive diarrhea and the suppressed gouty manifestations is fairly well established.[2]

Clinically, the compensatory activity of the bowels is usually demonstrable in these instances by the great pains and the tenesmus due to the chocolate-colored fecal masses laden with nuclein substances, concurring with a diminished amount of urine and a marked decline of vesical irritation and tenesmus.

The peculiar diarrheal attacks of exophthalmic goiter, like the profuse sweatings, must be regarded in the light of efforts at compensation. Furthermore, the excessive secretory activity of the sweat glands and the increased intestinal function, seem not only to compensate for one and the same systemic deficiency, but also to exercise the specific compensatory work alternately during certain stages of the affection. In acute cases of exophthalmic goiter, for instance, the sweatings are particularly apt to be frequent and exuberant while the diarrheal seizures are rather uncommon and of a mild character. In other cases of the malady, periods of sweating alternate with periods of diarrhea, and it is seldom when protracted sweatings occur for a number of times in a day, that a diarrheal attack supervenes.

The compensatory diarrhea of exophthalmic goiter sets in and terminates abruptly, and as a rule is not accompanied by pain. The attack generally lasts from one to three days and there are normally not any more free alvine discharges on each day then there are individual sweating seizures on the diarrhea-free days. The evacuations are softer and decidedly lighter-colored then in gout. If the diarrheal period lasts for five consecutive days or longer structural changes in the in-

1. This author (Verhandlungen d. XIV Congr. f. inn. Medicin, Wiesbaden, 1896), obtained from 100 grams dried meconium, in addition to alloxur bases, from 0.3 to 1.0 gram uric acid. He also points out that alloxur bodies may be demonstrated in the feces after a nuclein-free diet (milk regimen).

2. Hayem found in the villi extensive uratic deposits.

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testines will be encountered in the majority of instances. Especially will this be the case when there occur diurnally as many as twelve or more movements. Such pathologic changes are not the cause but the consequence of the compensatory attempt—they are complications keeping up the diarrhea beyond the compensatory needs which means that the patient has entered a stage of active decline. The diarrhea when confined within compensatory limits is nearly always followed by a temporary general improvement.

In Addison's disease two distinct forms of diarrhea may occur; the one form ensuing toward the end of the affection, colliquative in character and accompanied by severe colicky pains and often by melena, may quickly lead to either collapse, or delirium, coma and convulsions. It is entirely dependent on typical anatomic changes in the intestinal solitary follicles and Peyer's patches.

The other form, which is exhibited in but a small proportion of cases, supervenes in the earlier stages of the malady, and appears to be of a compensatory nature. In two exceedingly mild cases of the affection of which the one was under my observation for almost three years, the other for more than five years, there prevailed a moderate diarrhea of mushy consistency at frequent intervals. These diarrheas were usually followed by periods of systemic improvement, viz. greater energy and muscular resistance, diminished languor and increased appetite. Both the patients drew my attention to their almost unfailing general improvement after these diarrheal attacks. In the one patient there occurred partial reduction of pigmentation and the affection assumed a latent character; the other patient, apparently none the worse for the Addison's disease, succumbed to an intercurrent acute infectious disease.

Diarrhea is a frequent phenomenon in diabetes. Its relation to the latter may be twofold—it may be a symp-

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tom of the pathologic state underlying the diabetes, or it may be a result or complication of this. Diarrhea as a symptom of the diabetic substratum does not interest us in this consideration for it reflects only a more or less disturbed intestinal digestion. Diarrhea as a complication of diabetes may be due to a long-continued proteid-fat regimen in which case it is but an expression of an alimentary insufficiency, or it may be called forth by the rapid transmission of certain catabolic substances into the intestinal canal in which instance it may compensate for perverse plasmolytic or lipolytic processes. Be this as it may, there are a few indisputable facts in this connection, namely that a compensatory diabetic diarrhea takes its origin in the small intestines, that by its agency sugar may be excreted, and that during its presence and for some time afterward the intensity of the glycosuria becomes markedly diminished or the urine may even be rendered entirely free from sugar.[3]

It is, of course, impossible to explain how and why sugar has found its way into the intestinal tract of an individual just at the period when he is pursuing a rigid carbohydrate-free regimen. For granted that the proteid-fat diet is the cause of the diarrhea (as maintained by some observers), where are the sugar-forming elements coming from, and why is there a synchronous reduction or suspension of the glycosuria?

The occurrence of sugar in the feces, I dare say, should always be considered as of pathologic significance. On no occasion have I detected sugar in the feces of diabetics whose bowels functionated normally —I have never found it in other than diarrheal discharges.

The diarrheal stools in diabetes, however, do not always exhibit sugar, and I do not wish to be understood

3. I have repeatedly observed in diabetics that the urines rendered sugar-free by an attack of diarrhea are apt to exhibit a distinct reaction for acetone and diacetic acid which, soon after cessation of the diarrhea, can no longer be obtained.

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that the compensatory diarrheas in diabetes are characterized by their contents of sugar. Far from it, for I accept as efforts at compensation in the diabetic state all the diarrheas concurring with a reduction or suspension of the glycosuria, and which are being followed by marked, if but temporary systemic improvement including the dispersion of neuritic and endarteritic pains.

While it is true that diabetic coma is generally ushered in by an acute gastrointestinal disturbance, it is equally true that it may be averted by a diarrhea exerting compensatory function. There would be many more instances of diabetic coma, and it would often ensue much earlier in the course of diabetes, if a diarrhea rendering ineffectual the accumulated toxins did not supervene at the proper time. Of what nature these toxins are, we do not know. However, they do not belong to the acetone group, and the small amount of sugar which may be encountered in the diarrheal evacuations is not of toxic but of mere symptomatic significance. I have observed on more than one occasion that an attack of spontaneous diarrhea setting in during precomatose jactitation has prevented the further development of the coma.

Diarrhea occurring simultaneously with glycosuric augmentation and exacerbation of other diabetic phenomena—conditions not infrequently called forth by lesions in the descending and sigmoidal portions of the colon—of course exhibit no systemic compensatory qualities.

Of the second type of compensatory intestinal activity I will but mention the diarrheas following extensive burns of the skin and those concomitant with impaired or suppressed renal function.

Injury of a considerable area of the cutaneous surface by burns or scalds always gives rise to autotoxic manifestations. There may be retention of urine and

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various nervous phenomena as delirium, coma or a maniacal condition. The respiratory gas interchanges by the medium of the skin, compared with those taking place in the lungs, it is true, are diminutive, but a portion of such catabolic products as urea, uric acid, fatty acids, leucin, tyrosin, etc. leaves the organism by way of the integument. This is not the place to discuss whether or not extremely poisonous substances like hydrocyanic acid are generated in grave cases of burning, but it must not be forgotten that tegumentary activity includes also absorption of atmospheric oxygen, and that factors affecting the eliminative qualities of the skin also affect its absorptive properties.

In my book on the autotoxicoses,[4] from which some of the foregoing is quoted, I stated that when the cutaneous structures fail to exhale and discharge effete substances normally eliminated by them, the insufficiency may be overcome by inducing the other emunctories to vicarious activity, and that anything which in the face of diminished tegumentary function stimulates the general excretory work of the organism tends to prevent or to suppress autotoxic manifestations.

Now, inasmuch as renal activity is seriously interfered with in grave cases of burning of the skin, the diarrheas which then invariably supervene have to be looked on as compensatory in character. In many instances, the diarrheal compensation is effective either in averting autotoxic phenomena or, when these are already present, in holding them in check. This fact was brought home to me about eighteen years ago when I treated a two year old child who was terribly scalded over the entire abdomen. When I was summoned the little patient was unconscious, pulseless and the respirations were hardly noticeable. The rectal temperature was 103.5 F., and the bladder contained but

4. "The Autotoxicoses, Their Theory, Pathology and Treatment," by Heinrich Stern, Chicago: G. P. Engelhard & Co., 1906, pp. 64, 148 and 149.

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a few cubic centimeters of urine. While preparing a hypodermic injection to stimulate cardiorespiratory activity there occurred a copious watery discharge from the bowels. This was soon followed by a second and a third evacuation and (the hypodermic medication having been applied meantime) by an improvement of pulse and respiration. Diarrheal discharges prevailed for the next three or four days after which the diurnal urine was excreted in nearly normal amounts. Every third or fourth day thereafter for a period of about two months there occurred watery evacuations of the bowels and synchronous diminution of the urine. With the proper care, the apparently moribund child fully recovered after some months.

In grave cases of burning there supervenes occasionally a colliquative diarrhea at the foundation of which stands an ulcerative process in some part of the intestines. Such pathologic evacuations, which still further exhaust the already enfeebled organism, of course, have nothing in common with compensatory diarrheas.

Uremic diarrhea, as previously remarked, is the best known of all compensatory diarrheas. It is probably not so frequent an occurrence as are other phenomena of uremic causation, uremic vomiting for instance, nor does it seem to ensue any oftener than some of the compensatory intestinal evacuations of other systemic affections.

Uremic stools do not always present the same general characters; they may have a foul odor in which occasionally the scent of ammonium carbonate is recognizable, while at other times they are inodorous. The more repulsive the odor, the scantier, as a rule, is their amount, and the more frequent the evacuations the less dense is their consistency. They may be mushy, slimy or watery. When small in quantity the feces may be soft while the water together with which they are discharged from the bowels, appears to contain comparatively few fecal particles. The evacuations may ex-

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hibit light or dark coloration, not infrequently free mucus and but very rarely some blood.

Specific uremic diarrheas occur much more frequently in chronic than in acute states of uremia, and do not stand in any relationship to ulcerative processes in the intestines. Uremic ulcers of the bowels may occasion grave intestinal phenomena, which are, however, quite different from those of compensatory uremic diarrhea. The evacuations which are due to ulcerative intestinal states are often dysentery-like, very fetid and contain mostly blood and tissue shreds. There is sufficient pathologic evidence that compensatory uremic diarrheas, if continuing for protracted periods, may be accompanied by pronounced congestion and catarrhal exudation of the intestinal mucosa, but that they concur with ulcerative processes in the rarest of instances only. The cardinal etiologic difference between the two forms of uremic diarrhea is, that in the one the ulcerative process is the forerunner of the diarrheal condition[5] and that in the other the diarrhea stands either at the bottom of the morphologic changes of the intestinal mucous membrane, or that it is of synchronous or almost synchronous production with the latter, and the result of the self-same causes.

Compensatory uremic diarrhea is probably due to overstimulation of the intestinal nerves by the hyperosmotic blood carrying the products of normal and probably also of perverted catabolism. Whether this irrita-

5. Fischer (Virchow's Arch. cxxxiv, 134) and Grawitz (Deutsche med. Wchnschr., 1898 No. 20) maintain that uremic ulcers of the intestines are the result of the irritating action of the urinary decomposition products on the mucosa. This may be the case in exceptional instances, ordinarily, however, the amount of ammonium carbonate produced during a given period and remaining in intimate contact with the intestinal mucosa, is too small to produce necrobiotic processes. Be this as it may, the ulceration must precede the discharge by the feces of the material resulting from molecular death. It may be possible that ulcerative conditions develop in the course of a compensatory diarrhea, it is more plausible, however, that in certain instances of uremia the given factors favor the production of intestinal ulcers, and that an ulcerative process antedates the colliquative diarrhea.

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tion is caused by the altered blood *in toto,* or by the transudation *per se* of one or more of its constituents, we have no means of ascertaining. We know with certainty, however, that the decomposition products of urea give rise to a local irritation of the intestinal mucosa which may be followed by increased peristalsis and diarrhea. The mucosal congestion is probably of simultaneous production with the diarrheal symptom in most instances; this, at least, is the case after infusions of urea and other urinary constituents into the circulation in dogs. It is possible that the hyperosmotic state of the blood causes irritation of the cerebral cortex and that this irritation, transmitted to the intestinal nerves, occasions excessive peristaltic activity. Again, according to Landois,[6] augmented peristalsis may be the result of a strong irritation of the vasomotors by which the blood in the intestines is temporarily diminished.

Experiments pertaining to uremic diarrhea, conducted by Hirschler[7] have shown that among the urinary constituents which may call forth peristalsis, ammonium carbonate and creatin are not only very energetic peripheral but at the same time also central intestinal irritants, while urea, sodium chlorid and creatinin cause intestinal activity solely by means of peripheral stimulation. He further demonstrated that urea and ammonium carbonate may be looked on as etiologic factors of the uremic diarrhea.

That the uremic diarrhea arising in the absence of ulcerative changes is truly compensatory in character there can be little doubt. Uremic vomiting fulfils a similar compensatory mission which is plainly perceptible in certain advanced cases of chronic uremia when the ejected masses exhibit an urinous odor. This odor is due to ammonium carbonate and trimethylamin. Even the burning and dryness of the mouth and trachea

6. Die Uraemie, 1891, p. 130.
7. Jubilar-Arbeiten der Schüler Korányi's, Pester Med.-Chir. Presse, 1891, No. 30.

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of uremic patients Senator[8] ascribes to these irritating decomposition products of the nitrogenous urinary constituents.

The diarrheas with compensatory tendency occurring during the period of physiologic systemic decline form the third category of my classification. Strictly speaking, these diarrheas which comprise the diarrheal occurrences of normal old age, do not form a distinct group for themselves, but belong in part to the first, in part to the second category. Inasmuch, however, as it is not one specific function or organ but the more or less uniform decline of the entire physiologic activity and of the body structures in general which stands at the foundation of the compensatory diarrhea, we are well justified in considering the diarrheas of the aged in a class for themselves.

Old people are particularly prone to diarrheas, which are seemingly not dependent on atmospheric, alimentary, temperamental, occupational and localized enteric causes. These diarrheas become more frequent and pronounced the more the individual advances in age. In a certain proportion of instances free intestinal discharges have to be ascribed to structural and functional deterioration of the entire alimentary tract—these do not therefore concern us at this time—in other instances they are clearly of a compensatory nature, and this is a fact which has not received general recognition.

Women are oftener subject to the diarrheas of old age than men. The cessation of the menses seems to favor a disposition for diarrhea. There are many women who have never been affected with chronic diarrhea before the menopause. While most clinicians declare this diarrhea to be of the "nervous" type, I am forced to contend that a "nervous diarrhea" does not explain anything, and that there must be a retrogressive process at the bottom of these frequent watery evacuations, so long as the digestive and assimilative functions are per-

8. Die Erkrankungen der Nieren, 1902.

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formed in a normal manner and so long as there is no evidence of a structural alteration in the intestinal canal. What lies nearer then, than to assume that following the cessation of the catamenia there will ensue a hyperosmotic state of the blood and tissue fluids and that transudation therefrom will occur through those membranes which offer the most extended surface and least resistance, and these are the intestinal tissues.

It appears that the intestinal membranes retain a physiologic efficiency for a longer period than most other body structures. This, at least, is the case with their permeability which remains undisturbed, as a rule, long after the other emunctories have lost a great part of their own. It stands to reason therefore, that the intestinal tract of the aged has to perform more or less compensatory service all the time. Thévenon,[9] more than forty years ago, maintained that in health, when the general equilibrium is preserved, the products of the intestinal secretions are always more plentiful in the old than in the adult, that the internal tegument which is less exposed to continual external forces than the skin is physiologically less deteriorated than this, and that it is the tegument of the alimentary tract which compensates for the inactivity of the skin by removing a certain quantity of liquid from the economy.

Although modern research has demonstrated that the external integument is not to any greater extent affected by ectogenous causes than the alimentary tegument, and although the intestines are not internal organs in the sense that they are intrabiontic, Thévenon's observations, which were mostly made at the Salpêtrière, are in the main correct, and may be corroborated by any physician whose practice brings him in contact with old people, especially with the inmates of homes for the aged.

Since there exists a functional connection between the external and internal tegument, it is not surprising that old people, who perspire rarely, are subject to chronic

9. De la Diarrhée chez les Vieillards, Thèse de Paris, 1865.

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diarrheas. Again, pulmonary exhalation is greatly diminished in old age but the general systemic equilibrium is maintained by the compensatory action of the bowels.

The intestinal canal is beyond doubt the most efficient regulator of the shortcomings and disturbances constantly present or arising in the economy of the old. The compensatory action of the bowels tends to maintain the osmotic equilibrium, that is the interrelation of the physical conditions of the various body fluids, which is essential for the normal performance of the vital processes. This interrelation does not consist in the equality, but in the physiologic dissimilarity of the osmotic conditions in the different fluids of the organism, and it is often only by the increased function of the intestinal membranes that the osmotic equilibrium is preserved and the life of the individual prolonged.

The occurrence of an attack of compensatory diarrhea is nearly always a positive indication that there is no immediate danger for the life of the patient, and that terminal states like fatal dyspnea, convulsions and coma have been averted for the time being. Compensatory diarrhea is mostly a chronic condition, that is, wherever an attack has once ensued it is always apt to return. It is the frequent succession of the individual attacks which puts the stamp of chronicity on the compensatory diarrheas. The frequency of these attacks is rather a favorable omen, and the early establishment of compensatory diarrhea in the presence of perverted catabolism and insufficient excretion through the normal channels, let the prognosis of the case appear less gloomy. The elimination of all or nearly all the excrementitious substances by the intestines is liable to cause irritation and congestion of the mucosa—minor local disturbances which count little if the immediate salutary effect on the entire system be considered.

Of the compensatory diarrheas, not those supervening at a certain period and averting a fatal issue, but those recurring at frequent intervals and constituting a

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habitus diarrhoeicus and permitting the patient to live in comparative ease, are really the more important. However, while the former are known to the clinician the true nature of the latter is but rarely recognized at the proper time, and a treatment of suppression is instituted in nearly every instance. This interference, of course, is unjustified and irrational as a general rule and may speedily call forth a lethal termination of the case. Naturally, the prognostic outlook of instances thus treated is bad. Here is an example of such a case.

History.—On March 13, 1908, I saw in consultation Mrs. Susan S., aged 47, the mother of three children. The patient had been affected for some years with chronic parenchymatous nephritis, cardiac insufficiency and renal asthma. For the last two or three weeks she had had frequent watery discharges from the bowels, causing her physicians a good deal of anxiety, and concurrent marked diminution of the urinary flow, a fact in which, strangely, they seem not to have been interested. The output of urine for the past forty-two hours amounted to 180 c.c. The patient had received preparations of bismuth, tannin and opium for the diarrheal phenomenon.

Examination.—When I first examined her she was in a precarious condition: delirious, extremely weak, but mentally agitated, very dyspneic, edematous, pulse 124, arterial pressure 70 mg. Hg (Potain).

Treatment and Result.—I recommended discontinuance of all medication and the administration of high rectal saline injection, 1,500 c.c. every three hours. The few drugs which were given to the patient on the following days were mild diuretics. Nothing whatsoever was prescribed for the intestines but the carbohydrate ingesta were considerably reduced. The patient was kept in bed for about one week. The watery evacuations declined in the ratio in which the amount of the urine increased. The moment the kidneys eliminated a normal amount of urine with a fair degree of density the diarrheal discharges ceased on their own account. The patient has had a number of mild diarrheal attacks since for which the same treatment was given. It proved successful on every occasion. At this writing the patient is enjoying comparative freedom from the chronic uremic symptoms at Atlantic City.

Compensatory diarrheas of the type occurring in Graves' disease permit of a fair prognosis, so far as the

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life of the patient is concerned. Their periodical occurrence may be ushered in by an attack of indigestion, but the benign character of the diarrhea soon evinces itself by the temporary diminution or abatement of a number of distressing phenomena. In my experience, colliquative diarrheas are the exception in exophthalmic goiter, and anatomic changes of a pronounced degree, as large desquamative areas, submucous hemorrhages and ulcerative processes, so frequent in athyroidism and thyroidectomized animals, are very rare in this affection.

This general prognostic axiom concerning the compensatory diarrheas may be put forth. So long as a diarrheal process continues to compensate efficiently for loss of function of the skin, lungs, kidneys and the organs of internal secretion, or, in other words, so long as most of the effete and injurious material is removed from the organism by the medium of the bowels, the patient is in a satisfactory osmotic equilibrium and there is little immediate danger so far as life itself is concerned. On the other hand, the pathologic or artificial suppression of the diarrheal discharges may give occasion to grave symptoms and even cause death, in case the functionally deficient organs have not regained their activity meanwhile.

A true compensatory diarrhea should not be interfered with unless there is sufficient evidence that the localized intestinal irritation and hyperemia unduly prolong the increased peristalsis. Local intestinal treatment should be applied in preference to the ingestion of medicines which have to traverse from ten to twenty-five feet of gut before they reach the seat of the lesion. Rest in bed, application of heat to the abdomen, high rectal or colonic flushings with normal salt solution, and reduction of readily fermentable ingesta is all that is needed in ordinary cases of intestinal hyperirritation and congestion.

Inasmuch as a compensatory diarrhea is symptomatic of the insufficiency of excretory function in general, it

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indicates the points toward which treatment should be directed. Such treatment should tend to the stimulation of the catabolic processes and the regeneration of the eliminative qualities of the skin, lungs and kidneys.

DISCUSSION.

Dr. George N. Jack, Buffalo: I have happened on a few physiologic respiratory laws not in accord with authoritatively established opinions. 1. Lung tissue has a glandular structure, and performs a glandular function, serving the mortar-like purpose of holding the air tubes, blood vessels and lymphatics in close or functionating approximation. The lungs actually constitute two large irregular lymphangio-pneumatic glands. 2. The elasticity of the lungs is not so pronounced as it has been believed to be, neither does it constitute the expiratory force given it by existing authorities. 3. Lung tissue of itself is a coarse, friable, granular non-elastic tissue of little resistance and easily torn. 4. The only elastic tissue that acts directly on the lung substance is that of the visceral pleura, and the numerous small blood vessels or capillaries that so abundantly ramify through the lung. 5. The lung tissue itself is practically passive during both inspiration and expiration. 6. Owing to the vacuum-like pull between the visceral and parietal pleuræ, the lungs are, as it were, glued to the thoracic walls, from which they can not pull, and they are passively expanded and passively compressed by the action of these walls. 8. The existence of the pulmonary or lung blood pressure in the living subject tends to prevent the lungs from collapsing so readily and completely in the living subject as in the cadaver on admitting atmospheric air between the visceral and parietal pleuræ. 9. The air cells, minus the numerous small blood vessels in their walls, are not elastic, but they are very collapsible. The air cells do not contract to force out the inspired air, but they are made to collapse partially and thus caused to shove the inspired air out.

The normal expiratory partial collapse of the air cells in normal expiration is due to the pressure of the thoracic wall on the air cell, the recoil of the elastic visceral pleura or lung capsule, and capillaries of the air-cell wall, and to the expiratory changes in the pulmonary blood pressure, this blood pressure exerting its influence through the dense capillary network of blood vessels on the walls of the air cells.

Thus a high blood pressure retards the collapsibility of the air cells and favors expiratory dyspnea. The immediate relief from the dyspnea of certain forms of asthma and emphysema following perforation and entrance of air through the thoracic wall is due largely to its anti-blood aspirating effect, and resulting pulmonary blood pressure change.

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The apparent elasticity of lung tissue is due to a blood-pressure effect. The absence of blood pressure permits the lungs of the dead to collapse from the atmospheric pressure. The presence of blood pressure in the dense capillary network of blood vessels found on and practically constituting the thin walls of the air cells, is what gives to these cells of blood vessels or air cells an elastic effect in the living functionating lungs.

The general normal inspiratory rise of blood pressure produces an opening effect on the air cell which favors the entrance of air, while the normal expiratory reduction of blood pressure favors a softening of the tubular or vascular air-cell wall and thus favors the expiratory collapse of the blood vessel walled air cell. Lung tissue then performs a glandular function, while the air, air tubes and blood vessels do the respiration.

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EXPERIMENTS ON AN ASH-FREE DIET AND SALT METABOLISM

WITH ESPECIAL REFERENCE TO EDEMA IN DIABETES MELLITUS.

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The rôle played by the inorganic salts in diabetes mellitus has not attracted much attention. It was therefore a matter of considerable interest when Taylor[1] noted the presence of acetone and diacetic acid in the urine and acetone in the breath while he was living on an ash-free diet. The question was thus raised whether the withdrawal of salts from the diet might lead as a rule to the production of an acidosis in a healthy individual or accentuate an acidosis already existing in a diabetic patient. We have investigated the former of these points during the last year and have accumulated some information bearing on the latter point.

Two healthy students were placed on Taylor's ash-free diet, consisting of the whites of eighteen eggs, 200 gm. sugar and 120 gm. olive oil. After twelve and nine days respectively the chlorin excretion in the urine fell to 0.17 gm. Tests for acetone and diacetic acid in the urine were invariably negative. The results of these experiments showed no marked changes in metabolism, but rather represented the withdrawal of accessory salts from the body. They confirmed the views of

1. Taylor: Studies on an Ash-Free Diet, Univ. Calif. Pub., Pathology, 1904, i, No. 7, p. 71.

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earlier writers that it is practically impossible to diminish the chlorin of the body by more than 10 to 14 per cent., and demonstrated that the loss of water was proportionate to this. No remarkable symptoms appeared and those that occurred were less than would be expected from such a diet, even though it contained a normal quantity of salts. They gave no support to the view that the withdrawal of salts from the diet gives rise to an acidosis of the acetone type. A full account of these experiments will be found elsewhere.[2]

Evidence against the accentuation of an acidosis by the withdrawal of salt (not salts) was afforded by observations on a case of diabetes. This patient showed on the first few days of observation a positive carbohydrate balance of 60 gm. During a febrile attack this positive carbohydrate balance changed to a minus carbohydrate balance of the severest degree, not only all the carbohydrate in the diet appearing in the urine but nearly all the carbohydrate as well which theoretically could be formed from the protein metabolized in the body. On account of the severity of the case and the febrile condition of the patient the diet was of very simple character, and accidentally contained a very small quantity of salt. The chlorin was estimated repeatedly during the course of the case and on the fifteenth day was found to amount to but 1.7 gm. in twenty-four hours. Two days later it fell to 0.63 gm. and on the following day was 0.64 gm. Neither the symptoms nor the degree of acidosis, as determined by the ammonia, gave evidence of increased acid poisoning despite this low chlorin. We would not attach too much importance to these results, because the excretion of chlorin may be so variable a factor when there exists, as in this case, trouble with the kineys. Details of this case are given in the article above mentioned.[2] In Case 135, later described in this present paper.

2. Arch. Int. Med., July, 1908, i, 615.

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diabetic coma appeared when the salt was lowered in the diet, but the connection between the two phenomena would appear to be indirect, though by no means unimportant. Before entering further on the discussion of salt in diabetes, however, we wish to refer to the occurrence of edema in this disease.

The occurrence of edema in diabetes mellitus finds scant mention in the literature. Naunyn[3] says that edema is not a seldom occurrence in cachectic patients with severe diabetes, and is often an early symptom with patients having arteriosclerosis and myocardial degeneration, with or without the presence of albumin. It is occasionally present without cause. He mentions one case in which the edema disappeared as the patient became sugar-free on a diet containing 60 to 100 gm. bread. It is his impression (p. 261) that arteriosclerotic patients with diabetes mellitus seldom succumb to progressive dropsy, and very seldom present the picture of venous cardiac failure with its signs of passive congestion—persistent dyspnea, marked cyanosis, anasarca and fluid in the cavities of the body.

Von Noorden[4] writes: "In a few cases the patients have developed edema during the oat treatment, whereas otherwise, as we all know, the diabetics rarely exhibit edema." In another place[5] he makes this same statement apply to diabetics, even in the presence of valvular disease. Williamson[6] has observed anasarca in more than 5 per cent. of his diabetic patients. He records one case in particular in which it was not associated with albumin or cardiac or vascular trouble and cites Frerichs as having noted the same phenomenon in twenty-five out of four hundred cases. Roberts (cited by Williamson, p. 22) attributed the slight pitting over the tibiæ to the atonic state of the sub-

3. Naunyn, B.: Diabetes Mellitus, ed. 2, 1906.
4. von Noorden, Carl: Diabetes Mellitus, E. B. Treat & Co., 1905, p. 193.
5. Die Zuckerkrankheit, ed. 2, 1907, p. 169.
6. Diabetes Mellitus and its Treatment, 1898, p. 227.

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cutaneous tissue rather than to true edema; but Ebstein[7] ascribes it in a case of his own to the influence of the vascular nervous system.

Seven of our own diabetic patients have shown edema of greater or less extent, although at the time they presented very slight or no evidence whatsoever of disease of the kidneys or heart. In only two instances did the arteries present even moderate sclerosis. The cases were all of the severe type of diabetes. This was shown by the marked acidosis, minus carbohydrate balance, and the loss of forty to forty-six pounds during the previous course of the disease. Four of these patients have since died in typical diabetic coma; one of the remaining showed 7 gm. ammonia in the urine for twenty-four hours, and another 3.7 gm. ammonia. The edema in these patients occurred during a period in which there was a considerable restriction of the diet with a consequent fall in the excretion of sugar. Under such circumstances a simultaneous rise in the degree of acidosis was to be expected and such in fact took place. Along with the restriction of the diet sodium bicarbonate was administered either for the first time or in doses larger than those previously given. None of the patients died for some months after the edema was observed, although two showed distinct, clinical, premonitory signs of coma at this time. A brief summary of the various cases follows:

CASE 40.—The patient was a woman, aged 57, whose weight had fallen from a maximum of 152 pounds to 92 pounds. She then gained 21 pounds in twenty days in the spring of 1904 and presented edema. During this period the carbohydrates were restricted so that the excretion of sugar fell from a total of 141 gm. to 104 gm. There was a minus carbohydrate balance and diacetic acid was present in excessive amount. Sodium bicarbonate 12 or more gm. daily. There was a slight trace of albumin in the urine and occasionally casts. Premonitory signs of coma were present throughout, but death in coma did not take place until two months later.

7. Diabetes Mellitus. Unterleibskoliken und Oedeme in ihren Wechselbeziehungen, Ztschr. f. klin. Med., 1900, xl., 181.

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CASE 79.—The patient was a man, aged 43, whose weight had fallen from 180 pounds to 139 pounds. He gained 5½ pounds in ten days in September, 1904, and edema appeared. Five days before the first weight was taken there were 253 gm. sugar in the urine, but on the last days the sugar had fallen to 36 gm. There was a minus carbohydrate balance which persisted except for a few days later when the patient became sugar-free temporarily on a protein fat diet and the employment of vegetable days. Diacetic acid was absent at first, but soon appeared with the restriction of carbohydrates. Sodium bicarbonate was probably given in doses of 4 to 8 gm. The urine showed no casts and only the merest trace of albumin. One year and a half later, during a period of strict dieting and increase of alkali, the patient told me that his weight rose in the course of a few days 25 to 30 pounds and that there was general dropsy. The diacetic acid was then present in the urine in excessive quantities. Death occurred about six months later in coma.

CASE 101.—The patient was a man, aged 57 years, whose weight had fallen from 175 pounds to 132 pounds. He gained 13 pounds in twenty-two days in the autumn of 1905. Edema was marked at the time of maximum weight, but was not present before. In this interval the sugar in the urine decreased from 154 to 26 gm., and during the middle portion of the period there was a great increase in diacetic acid, and a minus carbohydrate balance. Sodium bicarbonate was given 8 to 12 gm. daily. The urine was usually free from casts and contained only a slight trace of albumin. Death occurred in coma a year and a half later.

CASE 132.—The patient was a man, aged 42, whose weight had fallen from 182 pounds to 128 pounds. He gained 4¾ pounds in ten days, November, 1907, only to lose the same in the following twenty-four hours. Edema was slight. During this period the sugar in the urine fell from 220 gm. to 60 gm. and the carbohydrates in the diet were lowered in about the same proportion. On admission the diacetic acid was recorded with a single + sign, but after ten days with ++++ signs. There was a minus carbohydrate balance. No sodium bicarbonate was given the first five days, but the latter five days it averaged 18 gm. There was a very slight trace of albumin and no casts.

CASE 164.—The patient was a man, aged 43, whose weight had fallen from 198 pounds to 132 pounds. He gained 11½ pounds in nine days in September, 1908, showing much edema. During this time the sugar in the urine fell from 180 gm.

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to 137 gm. and there was a corresponding lowering of carbohydrates. Diacetic acid was recorded as ++ at the start but on the last day was ++++. There was a minus carbohydrate balance. Sodium bicarbonate was given, 20 gm. daily. There was the merest trace of albumin in the urine and no casts.

CASE 147.—The patient was a man, aged 42, whose weight had fallen from 185 pounds to 151 pounds. He gained 12 pounds in twelve days in June, 1907, and edema appeared. During this time the sugar in the urine fell from 215 gm. to 51 gm. on the eleventh day, and diacetic acid increased from ++ to ++++. There was a minus carbohydrate balance. Sodium bicarbonate was given, 12 gm. daily. The urine showed the merest trace of albumin and no casts. Thirteen months later the patient returned to the hospital in a much worse condition. For convenience the case will be discussed later, but the data are recorded here.

TABLE 1.—CASE 147.

	Urine.			Diet.			
Date 1908.	Diacetic acid.	NH_3 gm.	Total Sugar gm.	Carb. gm.	$NaHCO_3$ gm.	Weight lbs.	Remarks.
2/25	+++	6	300	...	20	.....	
2/27	++++	5	118	92	20	127⅜	
2/28	++++	...	96	92	20	127⅞	Nausea, vomiting and threatening coma.
2/29	++++	...	113	68	24	127	
3/1	++++	...	149	123	24	122⅝	
3/2	++++	...	136	108	20	121⅝	
3/3	++++	...	131	103	20	124⅞	
3/4	++++	...	181	110	20	128	
3/5	++++	...	126	86	20	132⅝	Salt restricted.
3/6	++++	...	141	86	20	133⅝	
3/7	++++	5.6	166	...	20	133⅞	Patient allowed to visit a friend.
3/8	+++	7	229	...	20	133	

CASE 162.—The patient was a man, aged 30, whose weight had fallen from 154 to 113 pounds. He gained 8½ pounds in fourteen days in June, 1907, and edema appeared. The sugar in the urine amounted to 345 gm. about ten days previously, but was much less during the interval between the two dates on which he was weighed. Ammonia was present, 5 gm. Sodium bicarbonate was given, 16 gm. daily. The urine contained a slight trace of albumin and a moderate number of casts. Death occurred in coma five and one-half months later.

The factors which appeared most intimately connected with the development of edema in our seven

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cases were two—the restriction of carbohydrates and the administration of sodium bicarbonate. In our experience, however, the restriction of carbohydrates has never caused the appearance of edema in a mild case of diabetes. We have had an excellent opportunity to collect evidence on this point, because it has been our custom to weigh patients daily during the early period of observation, which is usually a period of restriction of diet as well. If the edema is dependent on restriction of carbohydrates, this must apply only to those cases like ours, which are of a severe type. To this aspect of the question we will later return.

The other factor — sodium bicarbonate — was considered by several of the patients themselves to be the cause of the edema, and for a time this seemed to us to be the most probable explanation. The first observation which threw doubt on this explanation occurred in the course of the treatment of Case 132. This patient gained, between November 14 and November 16 5¼ pounds, although no sodium bicarbonate was administered. During this time the diet was restricted from 215 gm. carbohydrate to 130 gm. Between Nov. 19, 1907, and Dec. 1, 1907, an average of 22 gm. of sodium bicarbonate was given daily, but the weight rose from only 129 to 129¾ pounds.

A further opportunity was afforded of determining the influence of sodium bicarbonate in the production of edema by a study of the following case:

Case 135.—The patient was a male, 34 years of age, who entered the hospital in January, 1908, in a most pitiable and cachectic condition, his weight having fallen from 138 to 88 pounds. He had been under our observation for nearly a year and a half, having developed diabetes three and one-half years before we first saw him. For a short time previous to admission he had given up on his own account the use of sodium bicarbonate, because he believed it was the cause of his edema. The diet on entrance consisted of milk, 1 pint, cream, ½ pint, fresh butter, 2 ounces, oatmeal (cooked), 1 gill, 4 eggs, meat, 10 ounces, potatoes, 8 ounces, 6 ounces of (cabbage,

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spinach, lettuce, tomatoes), apple, 4 ounces, orange, 4 ounces, olive oil, 1 ounce—without the addition of salt. It contained approximately 135 gm. carbohydrate, 110 gm. protein and 185 gm. fat. For the first four days no alkali was given. Twenty-five grams of sodium bicarbonate were then added to the diet. This was a little more than the quantity which the patient had taken intermittently for the two years up to the time he had omitted it before coming into the hospital. Two days after he began to take the alkali symptoms of coma became marked, and, despite the fact that the sodium bicarbonate was increased in quantity, death occurred two days later.

Not only was no edema to be noticed during the period of the administration of the alkali, but the weight, which had fallen 2½ pounds during the first four days after entrance, continued to fall, but at a much more rapid rate, namely, 3¼ pounds in the second four days. The quantity of carbohydrate was not reduced in the diet, but the amount of fats and protein was lowered because of the inability of the patient to take so much food. In the alkali period the quantity of liquids ingested was about 50 per cent. greater than during the first period, and exceeded the quantity excreted in the urine by 25 per cent. This was in contrast to the first period, when the quantity of liquids ingested and the volume of urine voided were approximately the same. Plenty of liquid was available, therefore, for the production of edema, yet it did not occur in the presence of sodium bicarbonate and a failing heart. The analytical data are presented in Table 2.

One of the points of interest in Table 2, and one which may have a bearing on the question of edema, is furnished by the chlorin excretion. This changed markedly as soon as sodium bicarbonate was administered, falling from an average of 6.3 gm. daily during the first period to 2 gm. daily in the second period. The constancy in the excretion of nitrogen and phosphates up to the alkali period was notable. As often occurs, the ammonia did not increase even in the pres-

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TABLE 2.—CASE 135.

	Intake.						Urine.								
Date. 1908.	$NaHCO_3$ gm.	Carb. gm.	Protein gm.	Fat gm.	Alcohol gm.	Liquids c.c.	Vol. c.c.	N gm.	NH_3 gm.	Acetone and diacetic acid gm.	β-oxy. acid gm.	P_2O_5 gm.	Cl. gm.	Sugar gm.	Weight lbs.
1/26	0	135	110	185	..	3500	3720	21.8	4.2	7.9	29	4.4	8.2	160	88¼
1/27	0	135	110	185	..	3500	3940	19.6	4.3	7.8	29	4.5	6.3	165	89¼
1/28	0	135	110	185	..	3500	3210	20.5	4.4	7.3	24	4.6	5.9	160	86¾
1/29	0	135	90	155	..	3500	3210	19.2	4.1	7.3	26	4.2	4.8	163	85¾
1/30	25	135	70	185	..	3500	3190	16.3	3.5	8.7	33	4.1	1.6	146	85
1/31	25	120	60	95	23	5370	4600	19.1	4.3	12.6	51	5.1	2.3	146	83¼
2/1	37	130	100	130	45	5250	4050	18.7	3.3	10.7	39	4.3	2.0	137	82¼
2/2	52	70	60	95	45	5370	3510	16.0	3.5	10.2	37	3.9	2.1	121	81¾
2/3	..	15	15	30	45	800	360	15.0	...	....	..	...	...	86	....

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ence of coma. The giving of 25 gm. sodium bicarbonate was certainly not sufficient reason for the lack of rise of ammonia with the need of the body for so much more alkali. The acetone and diacetic acid and the β-oxybutyric acid showed well the increasing acidosis, but it is worthy of note that the increase did not take place at first, although there was undoubtedly a restriction of 100 to 200 gm. of carbohydrates as compared with the diet before entrance. The analyses of the β-oxybutyric acid were made by the modification of Magnus-Levy's method recently suggested by Mr. Black. Duplicate analyses presented most satisfactory results, and we can not too highly recommend Mr. Black's procedure, which shortens the time required for the analysis of β-oxybutyric acid to a few hours.

The observations on the two cases above reported are distinctly against the view that sodium bicarbonate had anything to do with the production of edema in our cases.

The study of the action of sodium bicarbonate in a diabetic individual is difficult because the results of its administration may be so diverse. For example, we know that the administration of sodium bicarbonate to a severe diabetic leads to an increased excretion of β-oxybutyric acid in the form of its salt. This may not be an indifferent matter. Desgrez and Saggio[8] have shown that diacetic acid and more especially β-oxybutyric acid are distinctly harmful to the kidneys. It is therefore readily conceivable that the extra amount of these acids excreted following the use of sodium bicarbonate in severe cases of diabetes may so injure the kidney as to prevent its performing its ordinary functions, such as, for example, the excretion of salt. A retention of salt would of course in turn lead to a retention of water with an increase in body weight. The administration of sodium bicarbonate may on the other hand have a

8. Sur la novicité des composés acétoniques. Compt. rend. Soc. de biol., 1907, lxiii, 288. Reviewed in Centralbl. f. Stoffwechsel- u. Verdauungskr., 1908.

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totally different effect, since it is one of the best methods for removing chlorin and with it water from the body. In this event sodium bicarbonate would lower rather than increase body weight. Both of these actions might go on simultaneously. In that event it would depend on the quantity of salt in the body and the degree of injury to the kidneys whether the gain or loss of weight takes place. Still another variable enters into the problem, for both Magnus-Levy and we have observed in the study of patients with fatal diabetic coma that considerable quanitities of chlorin may be excreted by the intestines.

In order further to simplify the question of the etiology of edema in diabetes we determined to note the effect of the withdrawal and addition of salt to the diet of a diabetic patient. A favorable opportunity was afforded by observation of Case 135, above mentioned. The diet, which was constant, contained a comparatively small quantity of chlorin, though an amount amply sufficient for the usual needs of the body. During the first four days of the experiment the chlorin in the urine gradually decreased. This was presumably due to the small amount of chlorin in the diet as compared with that before entrance. The fall in chlorin excretion became much more rapid as soon as alkali was begun. The weights were parallel to the chlorin, falling slowly at first and then rapidly. Edema did not occur in the presence of a restriction of salt although the condition previously found favorable to its appearance —a marked diminution in the carbohydrate intake—was present. The explanation would thus apparently lie in the restriction of the salt in the diet. But the case suggests many interesting questions.

The patient remained in nearly as good condition during the first four days in the hospital as at entrance, but coincident with the administration of sodium bicarbonate, coincident with the fall of chlorin to a

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daily average of 2 gm., and coincident with the increasing loss of body weight, coma appeared. Might not these four factors be brought into connection? The sodium bicarbonate accelerated the removal of the accessory chlorin and water from the body, and it set free for elimination increased quantities of β-oxybutyric acid. Was not the percentage of this acid thereby increased in the remaining body fluids? In support of this view there are data available which show that the blood of diabetic patients in coma is more concentrated than normal. A diabetic patient on the verge of coma is well known to be in unstable equilibrium. At such a time the removal of nearly all the accessory water from the body must be of serious import.

Suggestive evidence that salt plays an important rôle in the production of edema in severe diabetes was given by Case 147 already reported. An examination of the data displayed in the table of that case will show that when this patient was on the verge of coma, the weight was at the lowest point. On this day in addition to the administration of considerable doses of sodium bicarbonate, as much as this particular patient's stomach would bear, we gave salt solution enemata, and he subsequently took a little more salt in the diet than is the rule. Coincident with his improvement, as was to be expected, there was a gain in weight, but this was so rapid that it is impossible to explain it otherwise than by the retention of water, which was later found by the appearance of edema. The gain in weight ceased when salt in his diet was restricted, although this was not done until he had replaced most of the floating water of the body. The improvement of the patient with comparatively small doses of sodium bicarbonate was unexpected and it suggested that the salt simultaneously administered might have had some contributory effect. It will be remembered in Magnus-Levy's remarkable case (Case 6) recovery from actual coma

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took place with the administration of large doses of sodium bicarbonate, some of which we infer was dissolved in normal salt solution. It is of interest too that in his case general dropsy, including ascites, developed. There was, however, albumin in the urine of his patient.

If the withdrawal of some of the salt from the diet of a severe case of diabetes prevents the occurrence of edema when the carbohydrates are being restricted, the administration of salt should lead to salt retention and gain in weight. We, therefore, gave salt in doses of 4 gm. twice daily to eight patients with diabetes. The weights of the patients were taken in the same clothes at the same hour (as a rule shortly before a meal) and after urination. For the sake of control the patients were weighed for several days preceding and following the salt period. The data are presented in the form of a table (Table 3). Two of the patients (11 and 112) presented marked acidosis, and it is at once evident that these were the only cases showing a material gain in weight in the salt period. They are patients who clinically correspond exactly with those in whom we previously had noted edema. Patient 105 was a boy with advanced diabetes of the severest type. He had not, however, lived on a very restricted diet for some time, and frequently took more than the moderate amount of carbohydrates allowed. Despite the severity of the disease acidosis was not marked, presumably because of his liberal diet. Patient 194 was a young girl with diabetes of only a few months' duration and of a mild form. The youngest patient with diabetes who in our experience has shown edema was 30 years of age. Patients 155, 8, 186 and 163 presented all the requirements for the production of edema, save that their diabetes was of a mild type without acidosis. These patients failed to gain weight in the salt period. These experiments require confirmation, but so far as they

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TABLE 3.—ADMINISTRATION OF SALT TO PATIENTS WITH DIABETES.

	Case 11.	Case 112.	Case 155.	Case 8.	Case 105.	Case 186.	Case 194.	Case 163.
Age	49	60	46	69	18	60	18	43
Carb. bal.	—	—60	+40	+35	—	St.+	+20	+87
NH_3	3.3 gm.	3.7 gm.	.....	.....	.....	.....	1.5 gm.	.....
Diacetic acid	++	++	0	0	++++	+	0	0
Weight (lbs.) during Control Period:								
Day 1	147	193	.....	153	111½	.....	.....	.....
2	147	193	173½	152 9/16	112⅜	176¾	110¼	170⅛
3	145	192½	173½	152⅝	111⅝	176¾	111	168½
4	145	193	173½	153	111¼	176¼	110	168¾
Weight (lbs.) during Salt Period:								
Day 5	147½	196¼	173½	153	110	176½	111¼	169
6	149	194	.....	153	110¾	178¼	112⅝	169⅝
7	148	196¼	173¾	152½	111	.....	112¼	169⅞
8	148	197	174½	.....	111⅜	177¾	112¼	170
Weight (lbs.) during Second Control Period:								
Day 9	.....	195½	175	152 1/16	112¼	181	111¼	169⅝
10	148	194	173½	151⅜	112⅜	180	111⅛	169
11	149	193½	173	151½	112½	179	111	169⅞
12	149	.....	173	152⅛	112½	179½	110½	169¼

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go they suggest that salt is an important factor in the edema of diabetic patients.

If one studies the quantity of chlorin eliminated by patients in diabetic coma it will be found as a rule to be slight. This may be due partly to starvation during the last few days of life, partly to the excretion of chlorin by the intestines, and also partly to the use of sodium bicarbonate in considerable amount during the period previous to the onset of coma, as well as to its employment in excessive amount in coma itself. The low chlorin excretion in coma is shown in Table 4.

TABLE 4.—CHLORIN EXCRETION IN COMA.

Author.	Case.	Duration of coma, days.	Total Cl. in coma, c.c.	Total vol. urine in coma, gm.	Remarks.
Magnus-Levy..	1	3	18.7	14,050	No alk. Died next day.
Magnus-Levy..	2	1½	1.30	6,590	Alk. ℞. Died.
Magnus-Levy..	3	3	18.49	10,060	No alk. Died.
Magnus-Levy..	5	2	5.24	5,400	Alk. ℞. Died next day.
Magnus-Levy..	6	5	13.22	36,825	500 gm. $NaHCO_3$. Recovered.
.....	.	6	14.40	9,475	Out of coma. Ascites.
.....	.	4	15.38	17,350	420 gm. $NaHCO_3$. Coma. Recovered.
Joslin.....	4	3	3.9	23,350	Alk. ℞. Died next day.
Joslin.....	135	3	6.4	15,990	Alk. ℞. Died next day.

A study of this table will show that the chlorin was low almost without exception when alkalies were administered, and high in those instances in which no alkalies were given. The only instance (Magnus-Levy, Case 6) in which the chlorin approached normal limits when alkalies were given recovered from the coma. In that case dropsy, including ascites, was present. One explanation of the appearance of coma in a severe case of diabetes mellitus would be as follows: The restriction of the carbohydrates in the diet leads to the non-oxidation of very considerable quantities of β-oxybutyric and diacetic acid, quantities much above those already being formed in the body. The elimination of these acids causes an irritation of the kidneys. This leads to

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the retention of salt and the production of edema in those individuals whose bodies contain considerable quantities of sodium chlorid. When the chlorin is low in the body, as is frequently the case, due in part to the long-continuous use of sodium bicarbonate, or to the lack of ingestion of food and even partial starvation in the last few days preceding coma, there is no extra salt to be retained, and consequently no edema appears. These latter patients therefore are especially prone to coma because the acids remaining in the body are in a more concentrated solution. Nature on the one hand is making every effort to remove the acids from the body by the kidneys bv means of the excretion of large quantities of urine, because only in this way can much β-oxybutyric acid be excreted, while on the other hand she is attempting to retain chlorin and water in the body to protect the normal concentration of body liquids.

The treatment of diabetic coma by the use of sodium bicarbonate has afforded unsatisfactory results, but prophylactically the use of alkalies appears to be of undoubted value. From the observations and experiments above recounted it would seem advisable to note the chlorin excretion in severe cases of diabetes, and when it is found low or when weight is falling yet the actual net caloric value of the food is sufficient, to add salt to the diet. In actual coma it would appear advantageous not only to administer large doses of alkalies, but also to give with them moderate quantities of salt. It is perfectly obvious that too much salt might do quite as much harm as too little, because by its administration too much liquid might be retained in the body, and the β-oxybutyric acid fail in excretion. Moderate quantities, however, would appear theoretically to be indicated. Only last year Folin suggested that the exclusive administration of one form of alkali was irrational and recommended a combination of salts.

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CONCLUSIONS.

1. The withdrawal of salt from the body does not lead to the production of acid intoxication of the diabetic type nor does it increase an acidosis already existing.

2. Edema in cases of diabetes mellitus presenting marked acidosis frequently occurs coincident with restriction of the carbohydrates in the diet.

3. This edema is not due to the simultaneous administration of sodium bicarbonate.

4. The edema is probably caused by the increased production of acids causing injury to the kidneys during excretion, thereby leading to retention of salt.

5. Patients in diabetic coma almost without exception present no signs of edema, and show diminished chlorin in the urine if alkalies are given.

6. The careful administration of salt along with sodium bicarbonate is recommended in the prophylactic and actual treatment of diabetic coma.

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DISCUSSION.

Dr. Alexander Lambert, New York: The cases that cause us the greatest worry and require the closest attention are those of diabetes mellitus in most unstable equilibrium. It would be interesting to know whether Dr. Joslin noticed at some time a diminution of the excretion and whether, in the slow drying-out process which the system must necessarily undergo, the amount of thirst diminished as the edema came on and the diminution in the water became apparent. In a discussion the previous evening the question came up in regard to sudden changes in diet in diabetes. I have never hesitated in making these sudden changes in diet, because I have not, as a rule, given alkali; whereas those who give alkalies in a patient with a severe acidosis find it unwise to make these sudden changes. Changing the salt content of the diet, the sodium chlorid and the sodium bicarbonate must be of great moment to these people. I have never seen anything but benefit result from these sudden changes in diet when I did not give alkalies, when the indications were evident, of course. In cases of long standing one can not hold the diabetic to too severe a diet. When too low a diet is given acidosis in many

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cases may come on, or be most prone to come on. It is hard to keep a diabetic contented with a restricted diet. If by the use of salt, as Dr. Joslin has suggested, we can relieve patients of some of their symptoms, keep them in better equilibrium, and keep the equilibrium in a more stable condition, I think that the observations made by Dr. Joslin are most valuable.

Dr. J. M. Allen, Liberty, Mo.: Over thirty years ago I found chronic inflammation and ulceration of the duodenum on postmortem examination in two patients that died from diabetes mellitus. Since then I have made postmortems in five additional cases, and in each found chronic inflammation and ulceration of the duodenum and no other pathologic condition, except the ordinary changes to be found in the kidney. In all I have treated twenty-seven cases; the clinical symptoms of each were the same as those of which I made postmortem examinations. Hence I conclude that diabetes mellitus is the result of faulty metabolism in the duodenum, caused by the pathologic condition mentioned. The practical abilities of the old masters in our profession are nowhere indicated with more force than in the diet list given to diabetics by Watson, Wood, Flint and others, which mainly consisted in albuminoids, thereby requiring but little function of the duodenum, and lessening the possibility of physiologic hyperemia. I read a paper on this subject and along these lines before the American Medical Association at its semi-centennial meeting at Philadelphia.

Dr. G. W. McCaskey, Fort Wayne, Ind.: The clinical importance of metabolism has increased greatly during the past few years, and the entire question of metabolism has assumed a very important place. One must look to the test-tube for a solution of many problems in connection with clinical medicine. I was particularly impressed by what Dr. Joslin stated about the four cases of severe diabetes in which there was a chlorid retention with a serous effusion; whereas in the mild cases there was none. This seems to me to point to the existence of an impaired renal permeability, at least for salines. It has been shown by von Noorden that as diabetes continues on for a period of time the sugar in the blood must be increased considerably over 0.1 per cent. before glycosuria takes place. Normally when there is over 0.1 per cent. glycosuria ensues. Whether this is conservative on the part of Nature, or whether it is the result of the chronic irritation, there is diminished permeability of the renal epithelium and the sugars and chlorids gradually increase in the blood.

Dr. Elliot P. Joslin, Boston: With the diminution in the excretion of urine there is a corresponding diminution in thirst. Recently Dr. Goodall and I published in the *Boston Medical and Surgical Journal* personal observations on the manner in which acidosis affects young and old diabetic pa-

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tients. We found that the latter succumbed to a degree of acidosis which young individuals could stand well. When an acidosis developed in a person of advanced years, or one past middle life, the prospect for life was less than when a corresponding degree of acidosis occurred in a young individual. Presumably it depended on the condition of the kidneys and their vulnerability. It is also interesting to know that it was only in the young persons that recovery from diabetic coma often occurred. The young person was capable of voiding large quantities of urine and so was able to wash the acids from the body. In one case nine quarts of urine were voided during recovery.

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THE FACTORS IN THE ESTIMATION OF BLOOD PRESSURE.

JOSEPH EICHBERG, M.D.
CINCINNATI.

The first factor in the interpretation of blood pressure must be a satisfactory instrument. It should, to be of service for general work, be portable, quick of adjustment and accurate. These qualities are possessed in eminent degree by the tonometer of Recklinghausen. It does not detract from the achievement of Riva-Rocci that later modifications have improved the technic; his merit will always lie in the impetus given to the study of blood pressure as a routine feature of the general examination; the aim now must be to analyze the findings properly.

The tonometer of Recklinghausen is based on the principle, first introduced into physical science by Bourdon and later incorporated into the kymograph of Fick, that if a very shallow, curved, elongated air chamber, fixed at one end, communicate at one end of the arc with a pressure apparatus, while the other is closed, any increase of pressure will be made manifest by a flattening or elongation of the arc, thereby imparting a certain movement to the end that is free. By a very simple device this movement of the air chamber is communicated to an axis, on which, guarded by a hair-spring, there is fastened a long needle, whose tip is made to move along a graduated scale, previously standardized, and the final figures are read off from the dial.

A notable advantage in the Recklinghausen apparatus is found in the pump. A metallic air-pump, constructed

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somewhat on the principle of the bicycle pump, is substituted for the ordinary double rubber bulb. The pump permits of increase or decrease of pressure at the will of the examiner; the instrument is at all times under perfect control; measurements can be made with greatest accuracy and promptly verified. By an ingenious arrangement of valves, easily controlled, this increase or diminution of pressure can be made to take place slowly. The whole apparatus is manipulated, without any force, by one hand, while the other is free to take the pulse. The pump is light, durable and only requires an occasional application of vaselin to valves and piston head.

The cuff is very broad, has a relatively small elastic chamber and a very strong band of thick canvas. It is applied by a buckle and strap, so that it can be snugly fitted to the arm. It is 12 cm. wide. The distention of the rubber pocket can never be very great, though the pressure run to considerable figures. The whole apparatus has, when packed, a weight of four and one-half pounds, and can be easily carried to the bedside of the patient.

The distinct advantage of the Recklinghausen apparatus is in its ability to measure both systolic and diastolic pressures. It will be seen that the mere determination of systolic pressure, though a step in advance, offers little help in the solution of clinical problems; the important thing is the relation of systolic and diastolic pressure. Aside from the actual pressure, measurable directly in centimeters of water, the tonometer makes it possible to observe the rhythm in time and power of the heart's contractions. It will frequently happen that the pulse seems perfectly regular at the wrist, when the ocular evidences of the slightly unequal movements of the needle will show the contrary; the pulse may seem to show an equal filling of the artery at each contraction, but the dial will record differences in this regard. Again, in many organic affections of the heart, a pecul-

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iar vibratile oscillation of the needle accompanies the excursions of the pulse, instead of the gradual rise and undulating decline, so that the tonometer offers all the advantages of a sphygmographic tracing, along with the information as to blood pressure.

Care must be taken that the examinations are not too long continued, for the interruption of the circulation in an extremity, if prolonged, will of itself cause changes in the blood pressure.

I start with this postulate: The arterial system has a capacity such that, if all arteries were perfectly limp and dilated, it could never be filled by the available amount of blood. The conditions necessary for a proper circulation are only secured by a certain permanent state of contraction common to all, or nearly all, of the arteries; a state of contraction still further increased with the functional inactivity of the parts supplied, and diminished, but never wholly relinquished, with the proper exercise of function. This brings the general conception of the circulation directly into line with what is known of the safeguarding devices with respect to the heart proper, and, as Gad has shown, with respect to the respiration, in which a state of partial but permanent inhibition always supplies a natural reserve to meet emergencies of all kinds.

This view is directly at variance with older physiologic doctrine. Thus Landois says:

> The system of blood vessels, with its many ramifications and subdivisions endowed everywhere with contractility and elasticity, is not only filled with blood; it is overfilled. Hence the mass of blood produces a certain pressure, which produces a stretching of the elastic vessel wall. This, of course, applies only to conditions during life; after death the muscular tissue of the vessel walls becomes relaxed and some fluid finds its way out into the tissue.

In the same way the doctrine that frequency of pulse-beat increases the blood pressure will doubtless receive revision. Foster says:

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If, while the force of the individual beats remains constant the frequency is increased or diminished, and, vice versa, if while the frequency remains the same the force is increased or diminished, the pressure is proportionately increased or diminished. This clearly must be the case, but obviously it is possible that the beats might, while more frequent, so lose in force, or while less frequent so increase in force that no difference in the mean pressure should result. And this, indeed, is not infrequently the case. So much so, that variations in the heart beat must always be looked on as a far less important factor of blood pressure than the peripheral resistance.

Clinical experience seems to demonstrate that actually the pressure is not influenced by the pulse-rate in the way that might be imagined. Weigert,[1] in a study of 241 cases of acute infectious diseases, found that the lowest pressures in many of these were observed not during the height of the fever, but in the first few days of returning normal temperature; at a period when the pulse was much slower than it had been; when the individual complained of a peculiar gone or good-for-nothing feeling, and when there was always some danger from any peculiar sudden effort. At this period there frequently is an abnormally slow pulse, coupled with this minimum pressure.

Conversely, I have recently had the opportunity of observing a case of paroxysmal tachycardia in a young man of 18, exceptionally tall and fairly well developed, whose heart, on January 14, when he presented himself, beat so fast and irregularly that the pulse could not be counted. The blood pressure in cm. of water, measured by the tonometer, was 122, diastolic 100. The patient was put to bed on light diet and took triple bromids with mild laxatives for two days, when the blood pressure was 128, diastolic 100, the pulse-rate being 72; January 24, the patient being now up and about and again attending a technical school, the pulse-rate was 84, the blood pressure was 134, the diastolic 96; April

1. Samml. klin. Vortr. (Volkmann's), No. 459.

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25, the pulse-rate was 102, the pressure 132, the diastolic 104. The pressure was practically the same at every stage, regardless of pulse frequency.

There is as yet no normal standard of blood pressure, and it is difficult to see how any uniform basis for comparison shall be found. Different observers have employed different instruments; from this fact alone there would naturally arise some discrepancy; but even with the same instrument the figures have not been even approximately uniform. Tables hitherto given have been based on observations of maximum or systolic pressure only, because it was impossible to get the diastolic pressure with the method employed. The Erlanger instrument is suitable only for hospital or office use; the tonometer of Recklinghausen is the only instrument thus far devised that conveniently gives us both of the data with certainty and promptness.

The accompanying table gives the figures as stated by different observers:

Landois, for larger mammalia and probably for man, 140-160 mm.
Faivre, direct measurement, 110-160 mm.
Albert, direct measurement, 100-160 mm.
Kuhe-Wiegandt, in uremic patient, 150 mm., direct measurement.
Basch, in temporals, 90-120 mm.; in radials, 110-160 mm.
Federn, 80-90 mm.
Bruce, 100-130 mm.
Tschienoff, in radial, 70-100 mm.; in tibial, 60-70 mm.
Huerthle, 100 mm.
Frey, in digital arteries, 100-110; in radials, 150-160 mm.
Eckert, in temporal, 175 mm.
Hensen, in 25 healthy men, aged 17-30, 137 mm.; in 30 women, aged 17-30, 132 mm.; normal range, 100-160 mm.
Gumprecht, in men, 140 mm.; in women, 120 mm.
Weiss, in men, 120 mm.; in women, 100 mm.
Schüle, 80-130 mm.
Neisser, 90-100 possible 160 mm.
Jellinek, in 500 soldiers, 100-160 mm., may be 180 mm.
Neu, 80-130 mm. (regards 130 as abnormal, most frequent 95-115 mm.).
Erlanger, systolic, 110 mm.; diastolic, 65 mm.
Graupner, 115-125 mm.
Sawada, 90-120 mm.
Schilling, 90-120 mm.
Janeway, 110-125 mm.
Sahli-Gassel, 135 mm., high limit of health.
Eichberg, in members of class in medical school, systolic, 86-120 mm.—diastolic, 56-88 mm.

No single reading should be considered a basis of final judgment. It is necessary to see the patient a

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number of times and to make the observations under diverse conditions, if possible, before estimating the blood pressure as an element of diagnosis. Error has arisen from neglect of this injunction, which has been especially insisted on by Sahli, Krehl and others.

To obtain a fair idea of the blood pressure normal to the individual, observations should be made with the patient fasting and again just after a meal; with the patient reclining and seated or standing; with the patient at rest and after a sudden muscular effort. This will give data for estimation of the actual work of the heart, and also an idea of its recuperative power, a feature of more significance in an estimate of the condition of the circulation than the mere value in figures. It may be assumed that, while an approximate standard exists, taken as an average of many observations as to what should constitute the normal pressure, this varies with each individual, and that it does so with the same individual at different times. The term "amplitude" is suggested by Klemperer for the difference between the systolic and diastolic pressure. Variations in amplitude in the same individual constitute a most important part of the study.

The amplitude increases for organic disease of the kidney, arteriosclerosis and aortic insufficiency. It diminishes for other organic diseases of the heart, affecting the valves or myocardium. It is interesting to note that in a healthy circulation the amplitude increases with moderate exercise, while every deficiency of the circulation manifests itself by a reduction of the amplitude, even when the systolic pressure is increased; this fact enables us to differentiate certain of the nervous disturbances of the heart from those due to organic mischief. In the case of the athlete with damaged heart, the initial amplitude was 114 c.c. in the recumbent position; in the sitting position, 108; after walking upstairs, 94; ten minutes later, 68. In one healthy young

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man the initial amplitude was 32; after walking, 48; in another test, initial amplitude was 36, after climbing stairs 46; on another occasion 30, after effort 48. According to Gerhardt, the systolic pressure in broken compensation is high, but the amplitude becomes small as the heart grows weak and again becomes greater as more powerful contractions are resumed.

The effect of exercise on the blood tension is a matter of daily personal experience. Any unusual effort makes us conscious of the beating of the heart. This implies an increase of work on the part of the heart, and an increase of arterial tension. The increase of tension is not directly proportioned to the work performed. Thus Masing[2] has shown that the labor of lifting 10 kg. produces a rise disproportionately greater than the labor of lifting 5 kg.

The fact that such an increase occurs makes it necessary to consider the previous conditions of the patient at the time of the observation. But the very fact of such increase as a normal reaction furnishes an important diagnostic aid. The healthy individual, after measured exercise, will present the increase of pressure, usually with increase of pulse-rate, the increase being more marked in the systolic than the diastolic pressure; but soon after the completion of the work, if not too greatly prolonged or too severe, the tension returns to the normal. For example, in a healthy young man, with an initial systolic blood pressure of 140 c.c., the pressure rose after walking up two flights of stairs to 170 c.c., but within five minutes was back again to 140 c.c. A striking contrast to this was offered in the case of a former circus athlete, now aged 53, who had a marked mitral insufficiency with arrhythmia and arteriosclerosis and a pulse of 96. The initial pressures here were, with the patient lying down, systolic 236 c.c., diastolic 122 c.c.; with the patient sitting, 240-132; after walk-

2. Deutsch. Arch. f. klin. Med., November, 1902, lxxiv, 253.

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ing up two flights of stairs, 216-122; ten minutes later, 190-122. Here the tension was not only lower immediately after the exercise than before, having fallen from 240 c.c. to 216 c.c., but it continued to decline when the patient was again at rest, and after fifteen minutes was still 50 c.c. lower than at first. A reaction of this kind always indicates a damaged myocardium.

Even in the presence of recognizable valvular lesion, the effect of such a test will, if the heart muscle be competent, give instant information. A man, aged 34, with an old mitral insufficiency, gave, while resting, systolic 168, diastolic 122; after exercise, systolic 188, diastolic 122; after five minutes, systolic 166; next day, while resting, systolic 158, diastolic 122, thus showing adequate compensation.

It is possible by practice gradually to increase the amount of work that can be performed, while still permitting the prompt return of the circulation to the state of normal tension, and this constitutes a proper system of training, as that term is generally understood. The injurious effects of training will inevitably appear sooner or later if such training carries the work beyond the point where a quick return to the normal tension is possible. The true limit of the training capacity of the individual is thus to be found in the interrogation of the arterial tension. Naturally the work that can be imposed on a damaged circulation and yet remain within its training capacity will always be less than that imposed upon a normal individual; in the selection of the test to be employed care and discrimination must always be exercised. Cases of advanced organic disease, of aneurism, of convalescence from exhausting acute disease, may be altogether unsuitable for its performance.

When the effort is prolonged but moderate, the pressure rises, but soon adjusts itself to a mean higher level, in which any slight additional effort produces no effect. Thus in the case of the young man just mentioned with

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a normal pressure of 140 c.c. the systolic pressure after walking one mile was 154 to 112 diastolic. Walking up two flights of stairs then made no difference, the pressure remaining at 154-112.

The quantity and viscosity of the blood necessarily influence the blood pressure. Moderate blood-letting up to 2.8 per cent. of body weight is not attended by any noteworthy decline of pressure. Blood-letting up to 4 or 6 per cent. of the body weight reduces the blood pressure to zero. The blood pressure is increased by any addition to the volume of the circulating fluid, as by injection of defibrinated blood, or normal salt solution, either directly into the veins or into the subcutaneous tissue, respectively. After copious meals there is also an increase of blood pressure, attributable in part to addition to the volume of circulating fluid. There is as yet no satisfactory means of determining the viscosity of the blood. Boveri[3] found that hypertension from adrenalin or tobacco was always accompanied by a notable increase of erythrocytes. Paul Arnold[4] also notes that chronic increase of the blood pressure, as a rule, leads to increase of red corpuscles and hemoglobin. Boveri remarked on the distinct parallelism between the viscosity of the blood and the number of erythrocytes, so that a polycythemia would usually indicate an increased viscosity.

The most important factor in the control of blood pressure is the nervous system. It had been known that almost every phenomenon connected with life, whether it be a physical or mental phenomenon, produced, temporarily at least, a modification of pressure over a larger or small portion of the vascular area. Taking the physiology of the nervous control for granted, it is of interest to note that recent experiments have added much interesting light. Curschmann[5] finds that the effect of pain-

3. Clin. med. ital., September, 1906.
4. Dissertation, Würzburg, 1907.
5. Berl. klin. Wchnschr., 1907, p. 132.

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ful faradic currents applied in such a way as to avoid motor points of irritation, in normal individuals, is generally to increase the blood pressure; in persons with organic or functional hypertension the increase is disproportionately greater. In organic analgesia the experiment produces no modification of pressure, nor is there any change in hysterical analgesia until the hysteria is relieved—thus seemingly proving that there is an actual sensory lesion in hysteria. Klemperer,[6] while admitting the influence of physical work in increasing the blood pressure, says that the amount of this increase is largely determined by psychic factors. Masing[7] determined that the increase of blood pressure with any given effort was less according as there was less determined effort of the will. Kiessling[8] shows that efforts which are unusual, requiring more mental concentration, are accompanied by a greater rise of blood pressure. Direct stimulation of the cortex in curarized animals is attended by a signal rise of blood pressure.[9] In man an analogous result follows hypnotic suggestion (Klemperer[6]). Here, with the muscles perfectly limp, the suggestion of work, such as mounting stairs or drawing a tight cork from a bottle, raised the pressure from 178 c.c. to 206 c.c. It then dropped to 176, and with a further suggestion rose to 210 c.c. The mere intention of doing work, the willing to do it, increased the pressure.

Passive movements, except those causing pressure on the thorax or abdomen, may be performed for a long time without increase of pressure. Klemperer says that the least factor in the increase of pressure attending any given work is due to the necessary muscular activity; the participation of the cerebral cortex is the principal cause. This fact may well explain the advantage

6. Ber. ü. d. Verhandl. d. Kong. f. innere Med., 1907.
7. Deutsch. Arch. f. klin. Med., 1902, lxxiv, 253.
8. Dissertation, Greifswald.
9. Weber: Arch. f. Anat. u. Physiol., supplement, 1906, p. 309.

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of passive movements in cases of heart lesion, either alone or, as at Nauheim, if coupled with effervescing baths, and gradually changed into resistance movements.

Dyspnea increases the blood pressure very materially.[10] This applies not only to acute suffocative conditions but to dyspnea of long standing. The amount of this increase varies greatly in different individuals, depending on the degree of the dyspnea and the power and adaptability of the heart. The walls of the vessels contract when the blood becomes distinctly venous in type. It is the increasing venosity of the blood, according to Landois, which causes the emptying of the arteries after death. The vasomotor center in the medulla is the direct agency in this phenomenon, the ganglionic cells being exceedingly sensitive to changes in the composition of the circulating fluid.

Contrary to what might be expected, acute infectious diseases have but little influence on the blood pressure. If we stop to reflect, the fact need cause no surprise, since the compensating mechanisms of the body are so abundantly provided that an acute condition, though it strain the limit of reserve, does not utterly exhaust it. Gerhardt[11] shows that in febrile diseases, as the heart grows weak, the arteries contract (probably under vasomotor influence), thus preserving the pressure. A very exhaustive study has lately been made by Weigert[1] of Dresden. In many of the acute infections the pressure fell during the height of the fever and returned to the normal as convalescence was established. There was no proportionate decline in pressure with increasing gravity of the symptoms. The report is based on a study of 241 cases, and the pressures recorded are all systolic. In typhoid fever there was a decline at the height of the fever. In pneumonia no change was noted at any stage, not even in the crisis. In scarlet fever without complication there was no change; the same was true of diph-

10. Jaeger, O.: Dissertation, Leipsic, 1906.
11. Samml. klin. Vortr. (Volkmann's), No. 470.

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theria without complications. The observations of the blood pressure furnished no certain prognostic indications nor suggestions for treatment. How little could be learned from the blood pressure with regard to the gravity of the case was shown in a case of ulcerative endocarditis, with general bacteriemia, in which six days before death the pressure was 140 mm.; three days later it was 95 mm.; then, despite increasing frequency of the pulse, it rose to 115 mm., and shortly before death attained 125 mm. In another case of ulcerative endocarditis with streptococci in the blood the pressure on the second day was 136 mm.; the next day it was 122; then it rose to 155 mm. on the tenth day, and on the eleventh, the day of the patient's death, it was 145.

However, Cook and Briggs[12] found in typhoid cases a hypertension increasing with complications, parallel to the severity of the disease and to deepening intoxication. The occurrence of perforation, confirmed by operation, was indicated by a sudden jump in pressure before the appearance of any other symptom, the pressure rising from 106 to 144; while in another case with seeming certainty of perforation, as shown by leucocytosis, rapid pulse and sharp abdominal pain, without rise of blood pressure, the operation failed to show any sign of perforation. Similarly, Teissier and others have found in the sudden increase of pressure a precursor of hemorrhage. Crile, too, found this increase of blood pressure in cases of perforation confirmed in four cases by operation or autopsy. In making this observation frequent tests will be indispensable, and only very marked, sudden fluctuations can be of value.

The acute condition may pass without notable change in blood pressure, but the subsequent history of these cases, as recently studied by Thayer in typhoid, shows that after the lapse of several years the damage done may become manifest. Thayer's patients all showed an

12. Johns Hopkins Hosp. Rep., xi.

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increase of blood pressure as compared with other individuals of the same age. Many had developed arteriosclerosis. The greatest rise was observed in the later decades.

Determination of a high or low pressure is in itself of no value. The lowest values compatible with life are found by Neu[13] to be from 40 to 45 mm., and these occur only with subnormal temperature in the moribund state, though Neu[13] has seen patients recover after the pressure had fallen as low as 50 mm. The greatest variation that has come under my personal observation was noted in the case of a shoemaker, aged 64, with arteriosclerosis, a man of temperate habits, with no recognizable lesion except a slight bronchitis, where the amplitude was 212 c.c., the systolic pressure being 394, the diastolic 182 c.c.

It is in chronic conditions that the study of blood pressure is of the greatest advantage for diagnostic and therapeutic purposes. Friedrich Müller states that the constant increase of blood pressure is the earliest symptom of a developing arteriosclerosis, and Groedel[14] maintains that the constant increase of blood pressure, in the absence of aortic insufficiency and of interstitial nephritis, is in itself sufficient to establish a diagnosis of arteriosclerosis. Hypertension does not necessarily exist in every case of arteriosclerosis; on the contrary, normal pressure may be present in advanced cases, but where the increased pressure is found the presence of arterial changes is indicated.

Hypertension, however, is not in itself a disease. Graupner[15] says that it is an accompanying or resulting symptom of many anomalies of nutrition — diabetes, gout, syphilis, chronic lead poisoning and certain kidney affections, all of which lead to changes in the splanchnic distribution. Changes may be present in the aorta, in

13. Experimentelle und klinische Blutdruck-Untersuchungen, Heidelberg, 1902.
14. Ber. ü. d. Verhandl. d. xxi, Kong. f. innere Med.
15. Berl. klin. Wchnschr., 1907, No. 15.

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the cerebral or brachial arteries, without any change in tension. Romberg and Hasenfeld have shown that hypertension occurs only when the arteries of the splanchnic territory are extensively involved. Sclerosis of the arteries is a very slowly progressive change. Its nature has been most exhaustively studied by Jores.[16] The association with nephritis has long been recognized. Groedel found in seventy-one cases of nephritis a minimum pressure of 130 mm., and more than half had a pressure of 170 mm. or more.

The general assumption has been that hypertension is in itself very dangerous, inasmuch as it leads to alteration of the vessel wall, possibly to rupture, or induces cardiac hypertrophy and subsequent dilatation, so that in every case baths, iodin compounds and nitrites should be used. This view is strongly combated by Krehl[17] and by Bier. They regard the high pressure as compensatory. In chronic kidney disease the high pressure causes a more rapid flow through the reduced vascular area in the kidney, and this more rapid flow allows of necessary elimination. In many cases, with a more effective action of the kidney, the pressure promptly declines. Krehl cautions against unnecessary interference with this beneficial automatic arrangement for maintaining the competency of the kidney, except in so far as regulation of the diet may reduce the proportion of waste products to a minimum, for reduction of blood pressure will retard the elimination from the kidney and increase the patient's danger. In six cases of chronic kidney disease with hypertension reported by Graupner the blood pressure fell as soon as the function of the kidney improved; the compensatory increase of tension was no longer necessary. Similarly Krehl regards the hypertension in arteriosclerosis as part of the natural regulation with which we should not interfere. On this point, however, issue may be taken, provided a healthy heart muscle

16. Wesen und Entwickelung der Arteriosklerose, Weisbaden, 1903, Bergmann.
17. Deutsch. med. Wchnschr., 1905, No. 7.

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exists. If the heart be insufficient, or if its power of adaptability be greatly reduced, then it is probable that the hypertension assists the circulation. But with a normal heart the increase of tension in arteriosclerosis is due to mechanical conditions, thickening of vessel walls, reduction of caliber, loss of elasticity—all purely mechanical obstacles, whose effects can be modified by treatment.

The indication of the necessity for treatment, for attempting to reduce the hypertension, is to be found in the response of the heart to blood-pressure tests after a measured amount of work. If the heart muscle still has a certain training capacity, then it does not require the compensatory hypertension. The question is always one of adaptability of the heart.

Many agencies reduce the blood tension. Warm, effervescent baths, as used in the natural state at Nauheim, are of most signal value and thousands are benefited annually; under their influence, if judiciously employed, the blood pressure increases to a physiologic maximum and then falls, while the functional capacity of the heart increases by combining the baths with exercise. The effect of iodin in arteriosclerosis is perhaps to be explained by the control which it exercises over the polycythemia, and by its reduction of the viscosity of the blood, rather than to any influence on the anatomic change. The effect of the nitrites is universally acknowledged.

It is in the direction of prevention, however, that we should most earnestly apply our efforts. With our knowledge of the influence of the nervous activity in the causation of the hypertension, with the recognized rôle of excessive waste products in the blood in the same direction, the treatment to be instituted lies more in educating the patient to right living than in the administration of medicine. Avoidance of alcohol and to-

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bacco, moderation in eating and drinking, proper hours of rest, and the elimination of excitement and nerve strain become the principal therapeutic measures. To cultivate repose is thus not only an obligation imposed by good breeding; it is an imperative law of physical health. The study of the blood pressure furnishes the guide as to the efficacy of the treatment, as well as to the time for its continuance. Assuredly it is not possible to agree with Romberg in this statement: "With regard to the measurement of blood pressure we thus have much more accurate information than formerly regarding one of the conditions under which the circulation is carried on. But even as no conclusions as to the efficacy of the circulation can be drawn from the height of the blood pressure, no clue as to the details of the mechanism is found in the composition of the blood pressure and its comparison with the maximum of pressure. These factors give no measure of the relative participation of heart and blood vessels in the existing changes of the circulation, because the extent of the pulsatile oscillation is influenced not only by the heart but by the tension and elasticity of the vessels, and the tension of the vessels is by no means in a fixed ratio to the maximum of pressure."

The following conclusions seem justified:

1. The routine interrogation of the blood pressure should constitute part of the regular examination of each case.

2. Both systolic and diastolic pressures are necessary in the solution of the problem.

3. Systolic values of more than 130 mm. call for further study.

4. The most important feature of the study of blood pressure is found in its behavior under tests with measured amount of work.

5. Increase of blood pressure is often conservative, and then calls for no interference.

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6. A pressure that is at all times above normal may be the only, as it often is the earliest, evidence of arteriosclerosis.

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DISCUSSION.

Dr. W. F. Dutton, Pittsburg: The etiology of hypertonic contraction readily resolves itself into two great divisions, the influence of the nervous system and the composition of the blood. I am not referring to the mechanical conception which would make the arteries mere elastic tubes but to that of living tissue. I have been experimenting with methylene blue. When administered in large doses a retention of the drug in the tissues takes place, owing to a disturbance of renal function, and manifests itself by a diminished excretion of the drug in the urine and feces. After a saturation of the tissues every additional dose is followed by a lessened functional activity. This effect is most apparent in the arteries, and it causes at once a hypertonic contraction and hyperemia of the renal capillaries as well as other pathologic conditions. This method is one to determine the condition of the arteries. The tightening or relaxation of the radial arteries is of clinical importance. The conception is false that the blood-pressure is heightened inside all hypertonically contracted blood vessels only. The two factors of the vessel wall and of the contained blood must be separated. There should be an estimation of the pressure inside of the artery, no matter what the thickness of the walls may be. Nervous reflex, however, may be due to blood impurity.

I do not believe that von Recklinghausen's instrument differs greatly from others. The only thing that can be depended on in its use is the estimation of the resistance of the blood. None of these instruments is perfect. The one, however, that I believe to be the most convenient for the general practitioner's use is that of Riva-Rocci as modified by Cook. The hypertonic, or the sclerotic or atheromatous condition of the arteries is determined by the sense of touch. I believe that the more the general practitioner practices this determination of the arterial condition by the sense of touch, the more perfect he will become—and more so than by the use of these complicated instruments. Arterial sclerosis and atheroma are totally different. Continued stimulation of the arterial wall leads to structural changes, and the fact that a fibrous hyperplasia of the tunica intima takes place shows that the vessel changes are not due to mere nerve influence, but to the blood itself. The intensity of internal changes in the kidneys indicates a presence of excrementitious substances in the blood seeking an outlet. There lies, in part, an explanation of vascular, cardiac, and renal changes. Most text-books endeavor to present the

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subject in such a way as to make one think that atheroma, sclerosis and hypertonic contraction are one and the same thing. But the surgeon might treat a broken leg for tumor of the brain just as well as the physician might treat atheroma for sclerosis.

Dr. N. S. Davis, Chicago: In certain arterial diseases the arterial wall still retains its power to contract; I have observed that other physicians often overlook this fact. It is a fact that not only healthy normal walls but diseased arterial walls possess this tonicity or power to contract. Furthermore, many times a diseased arterial wall has a greater degree of tonicity and power to contract, or is more easily stimulated to contract, than a healthy arterial wall. When the artery is compressed the cessation of the flow of blood through it depends not entirely on the pressure of the blood inside the artery, but first on the thickness and tonicity of the arterial wall—in other words, on the rigidity of the arterial wall; and second, on the size of the lumen of the artery. Therefore, when a hemomanometer is applied to an arm and the arteries in it compressed it must be remembered that the compressibility of the artery as well as the pressure of the blood within the artery is being measured. The so-called arterial tension really means the compressibility of the artery.

Dr. I. J. Wolf, Kansas City, Mo.: I am especially interested in two points that Dr. Eichberg brought out. First, mental influence is capable of producing a rise and fall in the blood pressure the same as physical labor. This is somewhat akin to what Parlow demonstrated regarding the work of the stomach: that the influence of the mind is as powerful in causing a flow of gastric juice as food itself. The other point emphasized, which I have often noticed in my clinical work, is that the increase in blood pressure is generally compensatory, and that to interfere with this compensatory increase in blood pressure is often dangerous. In such cases, when patients present themselves with a high blood pressure, the question is not so much what the blood pressure is at present, but what it has been before. If it was, for instance, 280 before and the kidneys were doing good work with such a blood pressure, it would certainly be dangerous to try to reduce it, or, if already lowered, to reduce it still further by the use of nitrites or the like. In such cases, though the blood pressure may seem dangerously high, the use of digitalis is more indicated and better able to remove untoward symptoms than the use of blood-pressure-reducing remedies. If, in addition, it is seen that through proper diet and hygiene the patient's blood pressure is not increased beyond the necessities of the case, the patient's welfare is guarded. High blood pressure does not necessarily mean a competent heart; nor does it exclude the use of digitalis.

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Dr. Joseph L. Miller, Chicago: In many cases of hypertension it is not necessary to institute any treatment. All no doubt will agree that most frequently these cases are due to the condition of the kidneys. The question then arises whether or not a lowering of the blood pressure reduces the elimination from the kidneys. There has been a considerable amount of work done on this subject and on the relation between the lowering of the blood pressure and the elimination from the kidneys. The most accurate work on this subject has shown that, when the blood pressure was reduced from 20 to 25 mm. of mercury, for example, and a careful determination of the elimination of water and solids from the urine was made covering a number of days, there was a decided reduction in the elimination of solids through the kidneys.

Dr. S. St. John Wright, Akron, Ohio: Blood pressure is only one of many pressures which modern methods of living affect. The changed relations existing between patient and physician demand consideration. In these days of meters and instruments of precision, which are now in most homes, the doctor must still be a leader as was the family doctor of old. He can not afford to be without apparatus. For the neurotic and morbidly introspective patient an array of apparatus might be injurious. In such a case the trained finger of the doctor, educated by the sphygmomanometer, will give him a working knowledge of the blood pressure and reassure the patient.

Dr. C. F. Hoover, Cleveland: There are instances in which lowered arterial tension in patients wih Bright's disease causes a profound depression. In cases of chronic interstitial nephritis—and this is a fact that I have verified a number of times—with the elimination of a very small amount of urine in twenty-four hours, the use of diuretin or caffein is not followed by diuresis; in these cases there is a high arterial tension and an oliguria. But when I lower the arterial tension there is a marked diuresis. Caffein or diuretin are without effect on the excretion of urine; but when trinitin is administered, lowering the arterial tension, diuresis occurs promptly. Dr. Wright wants a man of modern times and not of the old school. It is the use of the blood-pressure apparatus which teaches clinicians how to estimate blood pressure by touch.

Dr. Joseph Eichberg, Cincinnati: It was not with a view of measuring the blood pressure alone that I presented the instrument; but I wish to call attention to its availability in the routine examination of patients. It is not in determining the absolute blood pressure that much can be learned; not from its high or low reading, but from consideration of the blood pressure in connection with the symptoms. In the study of heart disease, the determination of

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the heart murmur alone really means nothing. After recognizing a certain cardiac murmur a proper analysis must necessarily determine its source. And so with the determination of the blood pressure; in hypertension only a proper study can determine whether the heart, the arteries or the nervous system is at fault. The most important feature in connection with the blood pressure is the determination of the compensatory action of the heart, the adaptability of the heart after a measured amount of exercise. Having determined the blood pressure of an individual at rest and in exercise, one should then note how the heart behaves. If the heart is competent, if fully able to compensate, the high pressure is not a dangerous factor. The criticism of the instrument which I present is well deserved in the main. The instrument of von Recklinghausen has the defects inherent in all instruments of this nature, but the errors are easily controlled. It does depend on the condition and tension of the metallic spring; but this element in error can be checked at any time by comparison with a standard gauge. The instrument is portable and can be readily carried to the bedside of a patient. It enables one to obtain promptly both the diastolic and the systolic pressure. It has manifest advantage over other instruments that require the use of mercury. Erlanger's instrument can not be carried around; its place is in the office or in the hospital ward.

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ACUTE INSUFFICIENCY OF THE SUPRA-RENALS.

R. S. LAVENSON, M.D.
PHILADELPHIA.

It is interesting that a condition looked on as one of considerable importance by the French clinicians is accorded but the most indifferent consideration by those of other countries. Hemorrhage of the adrenals has been generally recognized as a common pathologoic finding in still-born infants or those dying shortly after birth, and the literature of Italy, Germany and England contains occasional references to hemorrhage or other acute destructive lesions of the adrenals in adults. In none of the countries outside of France, however, has acute insufficiency of the adrenals become a factor in medical diagnosis in advanced life as well as in infants. It might be suggested that this state of affairs is but the result of the conservatism of the American, German, English and Italian clinicians contrasted with the somewhat more unstable, fanciful attitude of their French brethren. That a symptom-complex dependent on acute insufficiency of the adrenals does occur, however, in such a striking form as to demand clinical recognition is well exemplified by the case which I have to bring before you.

Patient.—A woman, admitted to the University Hospital, where in the capacity of clinical assistant to Dr. Stengel, I had the opportunity of observing her during her illness and of subsequently performing the postmortem examination. She was a widow, 44 years of age, white, and a native of Ireland. The few elements of her family history that were obtainable had no bearing on her present condition. Her previous history

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revealed the fact that during the past seven years she had had infrequent attacks of asthma, and that during the past two years she had been subject to occasional attacks of abdominal pain with vomiting. During the past two years she had lost slightly in weight.

History of Illness.—On November 30, shortly after eating breakfast, and while in comparatively good health, the patient had an attack of vomiting, with some pain in the epigastrium, at the same time she felt weak and prostrated. A half-hour later she drank a glass of water, when she again vomited. The pain in the epigastrium became more severe and the attacks of vomiting more frequent. During the afternoon there were frequent attacks of vomiting, and toward the evening the patient became slightly delirious. She was then seen by Dr. H. Kennedy Hill, who immediately sent her to the University Hospital. On admission to the hospital, temperature was 95, respiration 48, and no pulse could be felt. Vomiting had ceased by this time. The patient complained of pain in the epigastrium, and there was tenderness in this region and in the loins. The predominating symptoms were those of shock; the patient was extremely apathetic; her extremities were cold, the skin leaky and absolutely no radial pulse could be felt. During the earlier part of the next day the breathing became of the Cheyne-Stokes type.

Physical Examination.—The lungs were slightly emphysematous, and on respiration numerous dry râles could be heard. The upper border of the heart was on a level with the fourth rib; the right border at the right border of the sternum; the left border about a quarter of an inch outside of the left midclavicular line; the apex-beat was in the fifth interspace in the midclavicular; the cardiac sounds were weak and somewhat obscured by the respiratory râles; no murmurs could be detected. The tenderness in the epigastrium and in the loins persisted. There was slight rigidity of the abdominal wall, but no distention. The extremities were cold and slightly cyanosed.

Urinalysis.—Straw colored; slight brownish sediment; acid; specific gravity, 1002; no sugar or albumin; a small amount of mucus; a few leucocytes.

Blood Examination.—Hemoglobin, 61 per cent.; erythrocytes, 4,930,000; leucocytes, 52,800.

Clinical Course.—With vigorous stimulation during the day after admission, the patient reacted slightly, her temperature becoming 100 at noon on the day following admission. This reaction lasted for but a short time, the patient dying at 8

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o'clock in the evening following her admission, or about thirty-six hours after the onset of the illness. Respiration had remained in the neighborhood of 48; the radial pulse had at no time become palpable. As counted by auscultation, the heart beat from 120 to 140 times per minute.

It is almost needless to emphasize how impressive a clinical picture the patient presented—the suddenness of onset, the vomiting, the epigastric pain, the lumbar tenderness, and, above all, the profound shock formed a most striking group of symptoms. In the light of our knowledge at the time, it resembled most acute hemorrhagic pancreatitis, though the shock was more profound and the vomiting and epigastric tenderness less marked than would have been expected in this condition.

The autopsy revealed the interesting and unexpected nature of the affection. The following brief notes are abstracted:

Pathologic Report.—The lungs showed, macroscopically and microscopically, a moderate degree of emphysema with slight hypostatic congestion. The heart was of normal size; both ventricles were relaxed; the cavities and walls were of normal proportions: the valves were soft and competent; the coronary artery was slightly sclerotic; the muscle was somewhat grayer than normal. Microscopically, the heart muscle presented the picture of a slight, chronic fibrous myocarditis. The peritoneum was smooth and glistening. The uterus and appendages, aside from slight atrophy, presented no pathologic features. The kidneys were of normal size; their consistency considerably increased; the capsule stripped with some difficulty, but did not tear the kidney substance; the surface was slightly granular and showed a number of dark-based depressions and a few small cysts containing clear fluid. The microscopic features were characteristic of an arteriosclerotic, chronic interstitial nephritis of moderate degree. The stomach showed itself to be the seat of a chronic catarrhal gastritis. The intestines were without noteworthy characteristics, except for considerable venous congestion. The spleen was slightly enlarged and softer than normal. The liver was of normal size, its consistency slightly reduced; the organ was paler than normal, its structure somewhat obscured. The microscopic examination revealed fatty degeneration with early periportal fibrosis. The bile ducts were patulous; there were no gallstones. The pan-

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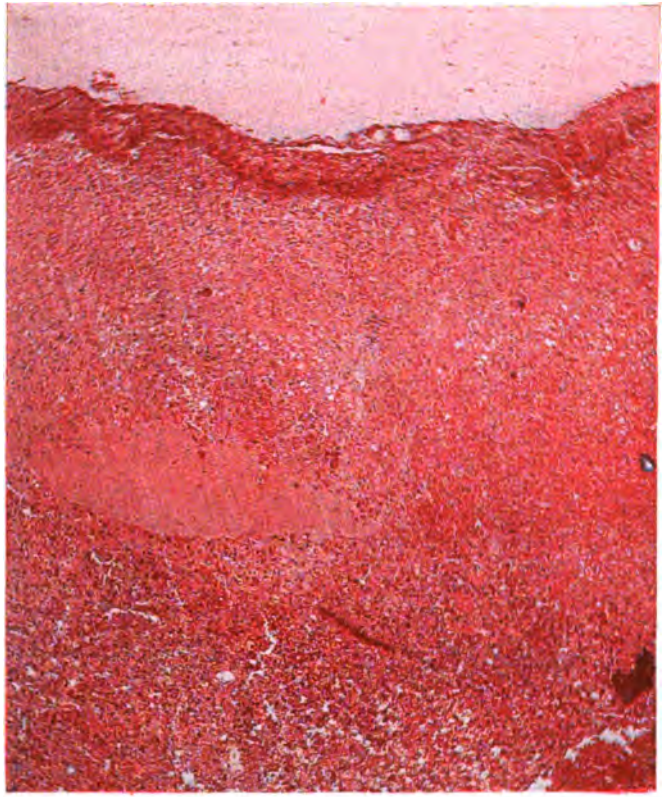
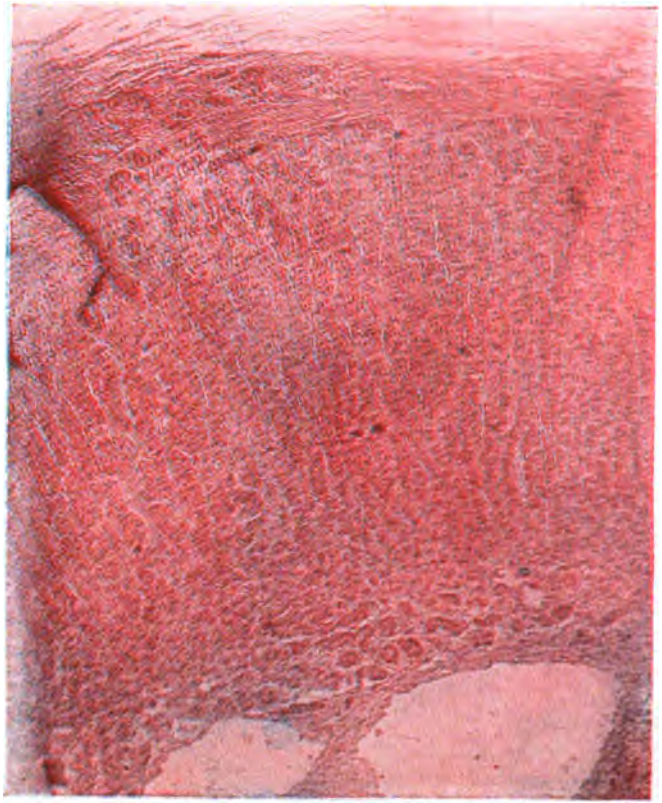


Lumière photomicrograph of necrotic suprarenal. Section stained with hematoxylin and eosin.



Lumière photomicrograph of normal suprarenal. Section stained with hematoxylin and eosin.

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creas was of normal size, the consistency increased, the structure somewhat obscured; on squeezing the organ, a few droplets of turbid, yellowish fluid were expressed from the smaller ducts; several pinhead size areas of fat necrosis were found in the peri-pancreatic fat. Microscopically, a distinct interlobular and intralobular fibrosis was seen, with some atrophy of the secreting cells; there was no necrosis; in the interlobular tissue, especially in the neighborhood of the ducts, there was a diffuse, polynuclear leucocytic infiltration of moderate degree. Both suprarenals were enlarged and soft, and presented on section a dark-red, homogeneous appearance; both suprarenal veins were thrombosed. Microscopically, there was almost complete destruction of the gland substance; with the exception of small, scattered islands, the parenchyma of the cortex stained a homogeneous pink with hematoxylin and eosin. Nuclei of the connective tissue cells of the stroma were preserved here and there, but scarcely any epithelial nuclei were visible. Scattered throughout this necrotic tissue were hemorrhagic extravasations of various size. There was considerable hemorrhage into the medulla, but less cellular and nuclear destruction than in the cortex. Cultures from the pancreas showed staphylococci, colon bacilli, and a non-identified Gram-positive bacillus. Cultures from the suprarenals were negative.

Pathologic Diagnosis.—Emphysema and hypostatic congestion of the lungs; chronic fibrous myocarditis, chronic interstitial nephritis; chronic catarrhal gastritis; acute splenic tumor; fatty degeneration of the liver, with beginning periportal cirrhosis; chronic pancreatitis, with acute interlobular suppurative pancreatitis; thrombosis of the suprarenal veins and acute hemorrhagic necrosis of the suprarenals.

Almost the only two conditions characterized by insufficiency of the suprarenals are hemorrhage and so-called adrenalitis. These two can be neither clinically or pathologically well differentiated in most cases. Adrenalitis is in the vast majority of cases not a true inflammation, as the term would imply, but a necrotic process, with which more or less hemorrhagic extravasation is always associated. When both necrosis and hemorrhage are present the two are generally the common results of the same condition, a vascular thrombosis. On the other hand, a number of the cases do present the clinical and pathologic features characteristic of

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simple hemorrhage. Many of these cases, by reason of the suddenness of the insult and the frankness of the hemorrhage, are appropriately termed adrenal apoplexies. The relation of suprarenal hemorrhage to acute hemorrhagic adrenalitis may be perhaps better understood by calling attention to the analogy that at least pathologically exists between them and pancreatic hemorrhage and acute hemorrhagic pancreatitis.

I have been able to find but two cases in which insufficiency of the adrenals was dependent on other pathologic lesions than hemorrhage or necrosis. One is the case of Janowski,[1] in which the two adrenals formed small abscesses above the two kidneys. The other is the case of Stursberg,[2] in which suppuration was found in both suprarenals of a woman suffering from Pott's disease. It is not improbable that the glands in this case were tuberculous.

Confining our attention then to necrosis and hemorrhage, let us determine what the factors are bearing on these two conditions. The extraordinarily rich vascularization of the organs naturally impresses itself as standing in some relation to the frequency of hemorrhage. The gland receives its blood supply from three sources, the aorta, the renal artery, and the arteries of the diaphragm. The arterioles and the capillaries from these sources form a dense network about the cells of the cortex, and the capillaries and venules finally unite in the inner cortical layers and medulla to form a single vein, which emerges at the hilus of the organ. The facts that such a large amount of blood unites to enter one vessel in the medulla, and that extensive hemorrhages usually seem to occur into the medulla, suggest that simple alterations in the blood supply or blood pressure of the organ may be the determining factors in the production of the hemorrhage. This hypothesis has been put forth as especially applicable to

1. Janowski: Gaz. lek., 1898, liv, 354.
2. Stursberg: Deutsch. med. Wchnschr., 1904, xxx, 1406.

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hemorrhage of the adrenals so frequently found in the new-born. The great increase in intra-abdominal pressure in the child, incident to the uterine contractions, and especially the pressure of the liver on the vena cava just above the suprarenals, have both been thought to be the direct cause of increasing the adrenal blood pressure sufficiently to induce hemorrhage. This view receives some support from the fact that when hemorrhage has occurred into only one of the suprarenals, it has been more frequently on the right than on the left (according to Hamill,[3] fifteen times in twenty-four cases), and the right vein enters the vena cava directly, while the left enters it through the renal vein. These relations would naturally subject the vessels of the right gland to greater pressure than the left in the presence of any cause obstructing the return of venous blood.

Chronic heart disease associated with passive congestion has been observed in a number of cases, and has thus been looked on as a causal factor.

Similarly, chronic pulmonary disease has been not infresuently found in these cases, and it is possible that the chronic passive congestion resulting therefrom has been an active factor in the production of hemorrhage.

A certain number of cases have been observed in which death has resulted after the occurrence of phenomena tending to a great increase in blood pressure, and in which, at autopsy, hemorrhage of the suprarenals was found. A striking example of this is a case reported by Ogle[4] of an epileptic dying after two weeks of almost continuous convulsions. At the autopsy hemorrhage into both suprarenals was discovered. I believe that it is not improbable that in some of the cases said to have manifested themselves clinically by convulsions these were the cause rather than the result of the hemorrhage, induced by the great increase in

3. Hamill: Arch. Pediat., 1901, xviii, 161.
4. Ogle: Tr. Path. Soc., London, 1863, xiv, 127.

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blood pressure incident to the convulsions. Duckworth[5] refers to a case in which the paroxysms of coughing in a child with pertussis apparently induced hemorrhages into both adrenals.

The great tendency to hemorrhage throughout the body in asphyxia, in all probability as the result of venous engorgement, has caused it to be looked on as one of the possible factors in the production of suprarenal hemorrhages, especially in the new-born. A factor emphasized by Spencer[6] as responsible for the greater frequency of suprarenal hemorrhages in infancy is the normal delicacy of the blood-vessel walls in this period of life.

Thus far we have dealt with only passive congestions. It has been asserted that active congestion also plays a rôle in the production of adrenal hemorrhage. One of the functions attributed to the suprarenal capsule is that of neutralizing toxins, and it is said that the functional activity of the gland in the presence of a toxic agent in the body so increases its blood supply as to lead to hemorrhage.

It is doubtful, however, if it is alone by increasing the blood supply to the gland that infections and intoxications act in inducing insufficiency of the suprarenals. In a number of cases organisms have been isolated directly from the adrenal glands, the seat of hemorrhage and necrosis. Klebs and Eppinger[7] isolated an organism in several cases of suprarenal hemorrhage in the new-born, which they called *Mona hemorrhagica*. Gaertner[8] isolated a bacillus resembling the colon bacillus, and Riesman[9] the *Staphylococcus albus* and *aureus* from four out of six cases occurring within a short space of time.

5. Duckworth: Twentieth Century Practice of Medicine, ii.
6. Spencer: Tr. Obst. Soc., Lond., 1891, xxxiii, 203.
7. Klebs and Eppinger: Boston Med. and Surg. Jour., 1891.
8. Gaertner: Arch. f. Kinderh., 1895.
9. Riesman, quoted by Hamill: Arch. Pediat., 1901, xviii, 161.

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Experimentally, hemorrhage and acute destructive lesions of the glands have been produced by Roux and Yersin[10] by inoculating rabbits and guinea-pigs with diphtheria bacilli; by Charrin and Langlois[11] with the *Bacillus pyocyaneus;* and by Roger[12] with the bacillus of Friedlander. Pettit,[13] Pilliet[14] and Wibaud[15] have confirmed these results. Oppenheim and Loeper[16] have produced similar results by injecting the toxins of Friedlander's bacillus, of the diphtheria bacillus and the tetanus bacillus, as well as by arsenic, phosphorus and mercury. Practically the same results were obtained by Bernard and Bigart[17] in injecting various metallic poisons.

Adrenal hemorrhage associated with general purpuric eruption can be looked on only as a visceral manifestation of a general hemorrhage tendency. As the purpuras of childhood are practically always infectious, the functional activity of the gland as the result of the infection, according to the above-mentioned hypothesis, probably increases its predisposition as a seat of hemorrhage.

Trauma does not seem to play a very important rôle in the production of acute destuctive suprarenal lesions. In but two cases, those of Canton[18] and Mattei,[19] does trauma seem to have been the cause of the adrenal hemorrhage found subsequently at autopsy. The secluded, well-protected position of the adrenals is probably the cause of its being so infrequently affected by trauma.

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10. Roux and Yersin: Ann. de l'Inst. Pasteur, 1889.
11. Charrin and Langlois: Compt. rend. Soc. biol., 1896, Series 10, iii.
12. Roger: Presse méd., 1894, i, 35.
13. Pettit: Thèse de Paris, 1896.
14. Pilliet: Arch. de physiol. norm. et path., Series 5, F. 7.
15. Wibaud: Etude des capsules surrénales dans les maladies infectieuses expérimentales, Brussels, 1897.
16. Oppenheim and Loeper: Arch. de méd. expér., 1901, xiii, 332.
17. Bernard and Bigart: Jour. de physiol. et de path. gén., 1902, iv, 1014.
18. Canton: Tr. Path. Soc. Lond., 1863, xiv, 257.
19. Mattei: (Case 2) Sperimentale, 1883, li, 386.

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In the cases of Arnaud,[20] Churton[21] and Dudgeon[22] adrenal hemorrhage was apparently induced by severe surface burns. In Dudgeon's and Arnaud's cases there were symptoms of adrenal insufficiency before death. This association suggests that which exists between surface burns and duodenal ulcer. Whether the adrenal lesion results from internal congestion, toxic products or embolism is quite as much open to question as the pathogenesis of duodenal ulcer.

Suppurative inflammations of adjacent organs has apparently been the cause of necrosis and hemorrhage of the suprarenals, with the clinical signs of insufficiency in three cases—my own and two of Arnaud's.[23] In one of Arnaud's cases the neighboring lesion was an abscess of the liver, in the other a suppurating hydatid cyst of the liver. In all three cases thrombosis of the adrenal veins was apparently the immediate cause of the changes in the glands. It is possible that pneumonia acts in the same way in producing acute insufficiency of the adrenals as to these lesions of neighboring abdominal viscera.

The appearance of the gland varies with the nature and extent of the lesion. Simple hemorrhages usually occur into the medulla of the organ. If of small size the hemorrhage merely distends the cortex slightly, producing but little destruction of its cellular elements. If of larger size it may so distend the organ that the cortex forms but a thin shell enclosing a large blood cyst. Rayer[24] records a case in which hemorrhage into a suprarenal gland resulted in a blood cyst weighing two kilos. Carrington[25] reports a case in which the suprarenals were transformed into cysts the size of large oranges, and in Routier's[26] case 1,600 cubic centi-

20. Arnaud: (Case 1) Arch. gén. de méd., 1900, clxxxvi.
21. Churton: Lancet, London, 1886, i, 245.
22. Dudgeon: (Case 2) Am. Jour. Med. Sc., 1904, cxxvii, 134.
23. Arnaud: (Cases 2 and 3) Arch. gén. de méd., 1900, clxxxvi, 5.
24. Rayer: (Case 1) Journal de l'expérience, 1837.
25. Carrington: Tr. Path. Soc., London, 1885, xxxvi, 454.
26. Routier: Bull. Soc. d'anat. de Paris, 1895, 73.

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meters of a blackish-brown fluid were evacuated from a suprarenal, the seat of hemorrhage. At times the capsule of the gland ruptures, permitting the escape of blood either into the surrounding retroperitoneal tissues or into the peritoneal cavity itself.

When hemorrhages are multiple and small they are usually found in the cortex rather than in the medulla. In such cases more or less necrosis of the epithelial elements of the cortex is usually present. The necrosis and hemorrhage may be the common result of the same cause, thrombosis, or the necrosis may be either the cause or the result of the hemorrhage. Judging from the pathologic features of my case, venous thrombosis results in extensive necrosis with but slight hemorrhage. In such cases the gland presents macroscopically a homogeneous, reddish-brown appearance and a microscopic picture similar to that described in the above pathologic notes of my case.

The fact that the lesions are at times limited more or less to either cortex or medulla has led to an attempt to classify the symptomatology according to the involvement of one or the other of these parts. Experimental evidence indicates that the functions of the cortex and medulla are different. The medulla seems to supply the elements having to do especially with the preservation of vascular tone, while the function of the cortex, aside probably from acting to an extent in a compensatory way for the medulla, appears to be the furnishing of an antitoxic agent to the body. In the majority of the cases of sudden death in adrenal insufficiency the hemorrhage does seem to have occurred into the medulla, but we are hardly justified in deducing from this fact the conclusion that this result attends destruction of only this portion of the gland. The functions of the adrenals are as yet too little understood and the limitations of the pathologic lesions involving them too poorly defined to warrant more than the statement that insults to the glands, regardless of their location or

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extent, may call forth certain profound symptoms such as will be described in the clinical discussion.

A study of the literature reveals a number of apparently incongruous relations requiring discussion. Numerous cases have been observed presenting the symptoms of acute suprarenal insufficiency in which only one of the glands was involved, the other being apparently normal. Why the compensatory action of the normal gland should not be capable of abolishing these symptoms is beyond the limitations of our pathologic knowledge to say. It is not improbable that our means of study are incapable of discovering lesions which, without destroying the morphologic integrity of the apparently normal organ, yet seriously interfere with its functions. A number of cases (those of Addison,[27] Goolden,[28] Carrington,[25] Greenhow,[29] and Mattei[30]) have been reported in which the symptoms of Addison's disease were presented and in which at autopsy acute adrenal lesions were found. In all of them the diagnosis of Addison's disease, as judged by the reported symptoms, is open to doubt, but even were it authentic it is rational to consider that a chronic degenerative process would only predispose the gland to hemorrhage or other acute process which by its promiience could obscure the recognition of the chronic changes. An interesting group of cases is that in which the signs of acute suprarenal insufficiency occur, followed shortly by death, and at autopsy the destructive lesions of a chronic process are found in the suprarenals.

In regard to such cases it must be emphasized that the degree of tissue destruction is not always a measure of functional incapacity, and it is very possible that only when the destructive process has reached a certain

27. Addison: On the Constitutional and Local Effects of Disease of the Suprarenal Bodies (Case 10), London, 1855.
28. Goolden: Lancet, London, 1857, ii, 266.
29. Greenhow: Lancet, London, 1877, i, 349.
30. Mattei: (Case 3) Sperimentale, 1883, ii, 386.

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degree, or involved certain elements, does it manifest itself clinically.

Since, as above stated, hemorrhage of the suprarenals and acute hemorrhagic adrenalitis can not be strictly differentiated either clinically or pathologically in the majority of cases, I shall not employ these two conditions as a basis for classification. The symptoms presented result from interference with the function of the adrenals, regardless of the agent inducing it. Even on the basis of the clinical phenomena I hesitate to attempt a classification for fear of confusing the reader in a maze of artificial grouping, for few of the cases conform to one type entirely distinct from the others. However, on the basis of the preponderance of one or another group of symptoms, I think that the following classification will serve as a basis for clinical consideration.

1. Cases of sudden onset with epigastric pain and tenderness, vomiting, profound prostration, feebleness and rapidity of pulse, coldness of extremities, lumbar tenderness, and at times diarrhea, and abdominal distention, followed within a few days by death. This is the symptom-complex that at times is called the peritoneal type of acute insufficiency of the adrenals, of which my case is a striking example. The literature of the subject contains a number of similar instances, among the most impressive of which are those of Stursberg,[2] Pritchard,[31] Mattei,[32] Arnaud,[33] Janowski[1] and Sotti.[34] The occurrence of the same group of symptoms in children is well exemplified by such cases as those of Batten,[35] Dudgeon,[22] and the two cases of Talbot.[36] There is a striking resemblance between the cases of this type and many cases of acute hemorrhagic pancreatitis. Judging from the one case that I have

31. Pritchard: Lancet, London, 1890, i, 750.
32. Mattei: Sperimentale, 1863, ii, 3.
33. Arnaud: (Case 1) Arch. gén. de méd., 1900, clxxxvi, 5.
34. Sotti: Policlinico, 1908, xv, Sem. méd., 1.
35. Batten: Tr. Path. Soc., London, 1893, xliv.
36. Talbot: St. Bath. Hosp. Rep., 1900, xxxvi, 207.

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observed, the shock is more profound, the lumbar tenderness more acute, and the epigastric pain and vomiting less pronounced in adrenalitis than is usually the case in acute hemorrhagic pancreatitis.

2. The asthenic type, in which the predominant feature is a profound asthenia ending within a few days in death. Instances of this type have been reported by Greenhow,[29] Murray,[37] Sicard[38] and Voisin and Norero,[39] all occurring in adults. In Sicard's case the asthenia was so pronounced as to give the case the appearance of an acute bulbo-spinal myasthenia. Interesting cases resembling those included in this group, except for their duration, are those reported by Marchand,[40] and Bernard and Heitz.[41] In Marchand's case the duration was three months, in Bernard and Heitz's case five months. In both of them there was an extreme degree of asthenia, and at autopsy simple atrophy of the adrenals was found in both cases. Bernard and Heitz employ their case to justify them in originating a condition which they term subacute insufficiency of the suprarenals.

3. The nervous type, in which the predominant symptoms have been either convulsions, as in the cases of Portal,[42] Valleix,[43] Parrot[44] and Droubaix;[45] or coma, as in the cases of Arnaud,[46] and Laginel-Lavastine;[47] or delirium, as in the cases of Mattei[48] and Ribadeau-Dumas and Bing;[49] or a typhoid state, as in the

37. Murray: Tr. Path. Soc., London, 1870, xxi, 395.
38. Sicard: Bull. Soc. méd. d'hôp. de Paris, 1904, xxi, 848.
39. Voisin and Norero: Bull. Soc. d'anat. de Paris, 1906, lxxxi, 320.
40. Marchand: Deutsch med. Wchnsch., 1903, xxix.
41. Bernard and Heitz: Tribune méd., 1904, New Series ii, 325.
42. Portal. quoted by Lieutaud: Historia anatomica, 1769, i, 285.
43. Valleix: Clinique des maladies des enfants nouveau-nés (Case 22), Paris, 1838.
44. Parrot: (Cases 10 and 11) Arch. gén. de méd., 1872, xix, 257.
45. Droubaix. Thèse de Paris (Case 1), 1887.
46. Arnaud: (Case 4) Arch. gén. de méd., 1900, clxxxvi, 5.
47. Laignel-Lavastine: Bull. Soc. anat. de Paris, 1902, lxxvii.
48. Mattei: (Case 1) Sperimentale, 1883, ii, 386.
49. Ribadeau-Dumas and Bing: (Case 2) Bull. Soc. anat. de Paris, 1904, lxxix, 477.

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cases of Virchow[50] and Kohler.[51] These varied symptoms have been noted in children, as well as in adults. In some of the cases in which convulsions have been a predominant feature I think it not improbable, as mentioned above, that they were the cause rather than the result of the injury to the adrenals.

4. Cases of sudden death. In this group I include the cases of sudden death in which at autopsy nothing except a destructive lesion of the adrenals, usually hemorrhage, has been found. It may be thought presumptuous in such cases to conclude that the sudden death was due to the adrenal lesion, but, realizing from experimental evidence and from the clinical evidence of the more protracted cases how profound an influence destruction or injury of the suprarenals has on life, I think that it is a justifiable inference. This I believe to be true of still-born infants in whom this lesion is found, as well as in cases of advanced life. Instances of this type have been reported by Rayer[52] and Goodhart,[53] and Hamill[3] has collected the cases occurring in still-born infants and children reported up to the year 1900.

5. Cases occurring in association with a purpuric eruption or hemorrhages into the abdominal viscera. Numerous cases of this type occurring in children are reported in the literature. I have been able to find none occurring in adults. Undoubtedly the hemorrhage into the suprarenals in these cases is but a manifestation of the general hemorrhage tendency as a result either of infection, or, in some cases, possibly of asphyxia. The English clinicians have been inclined to look on these cases as possible instances of hemorrhagic smallpox, especially by reason of the fact that many of the affected children have been unvaccinated.

50. Virchow, quoted by Lancereau: Dict. encycl. d. sc. méd., 1875, iii, 155.
51. Kohler: Dict. encycl. d. sc. méd., 1875, iii, 155.
52. Rayer, quoted by Roger: Jour. de l'expérience, 1837.
53. Goodhart: New Sydenham Society's Atlas of Pathology, 1879, ii, 50.

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As there is little else than this one fact in support of their view, I think it can not be looked on as a probable one.

Though the majority of cases permit themselves to be classified in one or another of the above groups, many are characterized by symptoms common to more than one group. The cases in which purpura is a prominent feature may present symptoms characteristic of the peritoneal or nervous type, and cases of the asthenic or nervous type may, in addition, present some symptoms belonging to the peritoneal type. Of all the symptoms the most constant and one of the most characteristic is a greater or less degree of asthenia. The occasional occurrence of two other symptoms is worthy of mention. They are tumor and the *ligne blanche* of Sergent.[54] A tumor, the result of suprarenal hemorrhage, is mentioned as having been determined during life in three instances. In one of Rayer's[24] cases it involved the right suprarenal and presented itself in the epigastrium. In Routier's[26] case a hemorrhage into the left suprarenal formed a palpable tumor in the left hypochondrium. In Leconte's[55] case there was a fluctuating tumor on each side of the mid-line extending from the hypochondrium to the iliac fossa. The *ligne blanche,* or white lines produced by stroking the skin with the finger, are looked on by Sergent as being of great diagnostic value in suprarenal insufficiency. They result from the temporary constriction of the relaxed vessels. As the majority of observers agree that they can be produced in various conditions attended by vasomotor relaxation, I can not agree with Sergent in looking on them as diagnostic of adrenal insufficiency. As clinical investigation has as yet advanced no pathognomonic signs of the condition, it is only when the symptoms observe a sufficiently characteristic grouping that the possibility of diagnosis during life can be enter-

54. Sergent: Bull. Soc. méd. d'hôp. de Paris, 1904, xxi, 380.
55. Leconte: Thèse de Paris (Case 48) 1897.

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tained. Attention should be paid to the relative frequency of the condition in the purpuras of childhood and during or shortly after the acute infections. An interesting case occurring subsequent to an acute infection is that reported by Sicard of a woman, 33 years of age, who shortly after the crisis in Friedlander's pneumonia suddenly manifested a most profound asthenia; death occurred within a few days, and at autopsy hemorrhage and necrosis of both adrenals was found. Bousset[56] asserts that he has recognized acute insufficiency of the suprarenals as indicated by asthenia, arterial hypotension, nausea, vomiting and diarrhea eight times in the course of various acute infections and that he has caused their subsidence by hypodermic injections of adrenalin. Due consideration must be paid to the apparent etiologic relationship that exists between acute suprarenal insufficiency and inflammations in the neighborhood of the suprarenals, surface burns, chronic heart or pulmonary disease, and any phenomenon tending to a great increase in internal blood pressure.

Such cases as those of Laignel-Lavastine and Arnaud claim for acute suprarenal insufficiency a rôle of some importance as a possible factor in apoplectiform deaths. Both of the patients were men, respectively 36 and 47 years of age, apparently previously in good health, who suddenly fell unconscious and died in coma, one twelve hours, the other forty-eight hours after the onset. At autopsy the only finding of note was hemorrhage into the suprarenals. When physiology has taught us more of the functions of the suprarenals, and when they are subjected to a more rigid routine postmortem examination, and when clinicians pay more attention to the facts already determined, I have no doubt that acute suprarenal insufficiency will assume a position of greater clinical importance than it has maintained in the past.

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56. Boussuet: Gaz. hebd. de méd. de Bordeaux, 1904, xix.

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THE BACTERIOLOGIC DIAGNOSIS OF TYPHOID FEVER.

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Since the introduction of modern laboratory aids in the recognition of typhoid fever the problem which has presented itself to practitioners of medicine is that of more accurate and earlier diagnosis. The demand for a scientifically accurate diagnosis is the outcome of the realization that clinical typhoid fever is a disease which may be caused by any one of several bacteria. The physician of the present day is no longer satisfied with the old term "enteric fever." He tries, so far as possible, to supplement his clinical diagnosis by an accurate bacteriologic diagnosis. The establishment of the bacteriologic diagnosis is only to be accomplished by the isolation of the specific organism infecting the individual patient.

From a practical standpoint the question of early diagnosis is of much greater importance than that of absolutely accurate diagnosis. To the individual patient early diagnosis in typhoid means better treatment, better nursing, perhaps more adequate domestic arrangements, and often a great saving of strength during the first stages of the disease. Moreover, if we are to have any specific method of treating typhoid, its value will probably depend to a great extent on the time at which its use is begun. In the sphere of preventive medicine the problem of the early diagnosis of typhoid has lately assumed enormous proportions. That the typhoid patient

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is a source of danger to the community during his sickness has long been recognized. That he may continue to disseminate the bacilli for months and years after his convalescence is now becoming a well-known fact. That he may, and doubtless often does, spread the contagion even before he shows any clinical symptoms of the disease, that the disease is infectious during the incubation period, has, however, only recently been proved. Conradi,[1] in a striking article, has demonstrated that the typhoid bacillus can be isolated from the blood of an apparently healthy individual, and has shown that in eighty-five cases of so-called "contact infection" the infection occurred in 58 per cent. of the cases during the first week. In the fight to limit the spread of typhoid fever the task of isolating and controlling the late dangerous cases, the chronic bacilli carriers, falls to a great extent on the public health authorities. The detection of the early bearers of contagion must, however, be the duty of the individual practitioner.

Although the bacillus of typhoid fever may be isolated from various sources, the only methods which have proved themselves to be of considerable value are the examinations of the urine, the stools and the blood. The first of these—the urine—has never come into special prominence as a routine procedure. The organisms can be isolated from the urine in about 25 per cent. of the cases, and often early in the disease; but this percentage of favorable results is hardly sufficient to warrant the method being used very extensively.

The examination of the stools as a diagnostic measure in typhoid appeared at one time to have a brilliant future. The conception of the disease as an intestinal infection went hand in hand with the idea that the dejecta swarmed with typhoid bacilli. The first difficulty encountered was the necessity of differentiating the typhoid from the colon bacillus. In answer to this need there was brought forward a long series of special

1. Deutsch. med. Wchnschr., 1907, p. 1684.

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culture media on which these organisms could be distinguished from one another with more or less accuracy. Some of these media were difficult to use, others comparatively simple. All of these methods, however, for their success depend on being used by skilled bacteriologists; and even so, the results obtained by them have not, on the whole, been favorable. In the hands of some observers they have done well, and there are many series of cases in which the bacilli have been isolated from a large percentage of the stools. Other equally good workers have failed to confirm these results and have only been able to find them in a comparatively small proportion of their cases. The conflicting reports as to the frequency of the presence of the bacilli in the feces are, however, at least partially explained in the light of our present knowledge of the disease. If, instead of regarding typhoid as a primary intestinal infection, we regard it as a primary septicemia, which usually has secondary intestinal lesions, with a secondary infection of the gall bladder, the uncertainty of finding the organisms in the stools is more easily accounted for. There is good reason to believe that the intestine and its contents form a very poor culture medium for the typhoid bacillus, for autopsy may show a gall bladder with bile so infected with typhoid bacilli that a single drop will give hundreds of colonies, while cultures from just below the ampulla of Vater, and from the intestinal contents at different points down to the cecum, will not show the presence of a single typhoid colony. It is possible, on the other hand, that the organisms growing in the gall bladder from time to time may be discharged into the intestine in such large numbers that many of them survive the passage of the intestine and may be isolated from the feces. It is a clinical fact that many negative examinations in a case may be followed finally by a positive examination, thus making the element of luck a prominent factor in the value of the process. The different results obtained by various observers may be ac-

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counted for also in some degree by the viability of the special race of organisms infecting the case. It is probable that some races of the typhoid bacillus are much more resistant to the hostile conditions in the intestine than are others. An analysis of the cases in which the organisms have been recovered from the stools shows that this method of diagnosis may often be useful in early as well as in late stages of the disease, but the difficulty of the technic, together with the relative uncertainty of the results, makes the method of comparatively small value as a routine procedure. The examination of the stools is, on the whole, chiefly important in the recognition of chronic bacilli carriers.

If typhoid fever is primarily a septicemia, it is natural to seek for the first signs of the disease in the blood itself. Since Castellani[2] first isolated the typhoid bacillus from the blood of a patient in 1899 the numbers of workers with blood cultural methods has shown a steady increase from year to year, and the literature on this branch of diagnosis has lately exceeded any other. Whereas the first reports on the subject were rather of bacteriologic and pathologic interest, the larger series of cases which have since been collected have shown that the method is of clinical value as well, and have begun to establish it on a practical basis.

The technic which has been most commonly used in making blood cultures has been thoroughly to clean the patient's arm and to take with a syringe about 10 c.c. of blood from one of the veins at the bend of the elbow. The blood is then distributed into several flasks of bouillon and diluted by the medium to such an extent that its bactericidal properties are overcome. Although this method has given excellent results in many hundreds of cases, there is no wonder that it has never become a routine procedure outside of a comparatively few large hospitals. It is distinctly a laboratory rather

2. Zentrlbl. f. Bakt., 1902, xxxi, p. 477.

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than a clinical method. Apart from the necessity of having a more or less trained bacteriologist to work out the culture, there are marked objections to the method itself. The culture medium is too bulky; it is often inconvenient to carry flasks of bouillon to the bedside. Then the technic of drawing the blood is not always simple. In fat persons, or in those with small vessels, it is at times almost impossible to insert the point of the needle into a vein. Of more importance, however, is the fact that to the patient and to the family the method must always appear to be a somewhat radical procedure. This is alone sufficient to limit the extent to which even a measure of recognized value will be used as a routine practice.

In order that any diagnostic method shall be accepted by practitioners in general, it must be stripped of all its technical difficulties and reduced to its simplest terms. Toward the accomplishment of this, and toward making the blood culture a practical aid in the diagnosis of typhoid fever, there has been much advance in the last few years. The first step of importance was the introduction by Conradi,[3] in 1906, of ox bile as a culture medium to replace bouillon. The peculiar advantage claimed for the new medium was that the bile salts prevent the coagulation of blood and the formation of bactericidal elements in the blood serum. Whether or not this explains the whole of the action of bile has been doubted. However, from the frequency with which the gall bladder is found infected at autopsy, and from the fact that in chronic bacilli carriers the gall bladder is the usual seat of infection, it is evident that bile must be especially well suited for the growth of the typhoid bacillus. By Conradi's original method, test tubes containing a mixture of ox bile with peptone and glycerin were used. The peptone was added to increase the growth and to aid in preventing coagulation of the blood. The glycerin was

3. Deutsch. med. Wchnschr., 1906, p. 58.

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to limit the growth of saprophytes. Kayser,[4] however, later demonstrated that as good results can be obtained from the use of pure ox bile alone, and he showed that if the blood added to the medium contains even as few as 2 or 4 bacilli the cultures after incubation will give a profuse growth. Working on another line toward a practical blood-cultural method, Müller and Gräf[5] have reported a series of cases in which they used small amounts of coagulated blood sent to the public laboratory for agglutination tests. After separating the clot from the serum, they used the latter for the agglutination, and the former they rubbed over the surface of Drigalski-Conradi plates. The plates were then incubated, and in 360 cases, including convalescents and chronic bacilli carriers, they were able to isolate the organism in 110, including 10 cases of infection with the paratyphoid bacillus. The disadvantage of such a plate method is that there is no increase in the number of organisms, and if not numerous they might be overlooked or overgrown by saprophytes. Fornet[6] has devised a method analogous to that of Kayser, in which he also uses the clot of blood sent in to be tested for the agglutination reaction, planting it in bile, and examining the culture after incubation. Of a series of 19 cases, 14 gave positive results. It is not expected that this will replace the technic of Conradi and Kayser, but it is a valuable method when it is impossible to get the uncoagulated blood into bile.

Of these various simplified blood cultural methods, one of the most satisfactory is the use of the medium of Kayser with small amounts of blood obtained from the patient's ear.[7] The technic is as follows: The lobe of the ear, after being carefully cleansed with sterile gauze and alcohol, is pricked rather deeply with a small lancet-pointed knife, the blood squeezed out drop

4. Kayser: Münch. med. Wchnschr., 1906, pp. 823 and 1953.
5. Zentribl. f. Bakt., 1907, xliii, p. 856.
6. Münch. med. Wchnschr., 1906, p. 1053.
7. Peabody: Arch. Int. Med., 1908, i, p. 149.

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by drop, and allowed to run into a test tube containing about 5 c.c. of plain, sterile ox-bile. It is usually easy to collect 2 c.c. of blood without any inconvenience to the patient. The mixture of blood and bile is then placed in the incubator at 37° C. for from 12 to 15 hours, after which a few loopfuls are transferred to a tube of Löffler's blood serum. In some cases, examination of a drop of the original bile culture after incubation shows the presence of a motile bacillus, but more often this is better demonstrated in the water of condensation of the blood-serum tube after about five hours. The presence of a motile bacillus is in itself excellent evidence in favor of an infection by one of the typhoid group; but in order to prove the organisms it is customary to test them for their cultural characteristics and for the agglutination reaction.

That this simplified method is one of clinical value has been proved many times. At the Massachusetts General Hospital, where it has been used as a routine measure in all cases of typhoid during the past few months, it has been the means of establishing the diagnosis in 55 of 82 cases examined. In 28 per cent. of the cases the culture gave the diagnosis before the agglutination test. In the first week the culture was positive in all of 17 cases; in the second week, in 70.2 per cent. of 37 cases, and in the third and fourth weeks, in 42.8 per cent. of 28 cases. The agglutination test was positive in 52.9 per cent. of the cases in the first week, in 67.5 per cent. in the second week, and in 82.1 per cent. in the third and fourth weeks. The results are similar to those obtained in larger series of cases, in which the old method of taking a greater amount of blood from a vein has been used.

It is thus evident that in the ox-bile culture method we have a measure of considerable diagnostic importance in the early stages of typhoid fever. It is, moreover, a method which can be used, not only by trained bacteriologists, but by any practitioner. When a man

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can not do his own bacteriologic work the culture may be sent to a laboratory to be worked out. In Germany some of the large chemical firms have put on sale tubes of bile so sealed that they can be sent through the mail to the public laboratories, where the cultures are incubated and the diagnosis made in the same way in which the public health laboratories in this country perform the agglutination reaction. The physician merely has to prick the patient's ear, collect the blood, and put the tube in the mail. The technic is thus only slightly more troublesome than that of the Widal reaction, and when it is considered how valuable the method is in making an early and accurate diagnosis it would seem that the blood culture must assume a major rôle in the future.

Of all laboratory methods in the diagnosis of typhoid fever there is none which has been used so extensively, or has given such excellent results in the hands of many clinical observers, as has the agglutination reaction. That it has been generally adopted the world over is due to its high degree of accuracy combined with its simplicity. The establishment of public laboratories, where samples of blood are examined for individual practitioners, has brought the test within the reach of a vast number of physicians. While, however, the reaction has proved itself of inestimable value, there are certain important drawbacks to its use. The chief of these is that the agglutination reaction is often late in making its appearance. It is frequently not obtained during the first week of the disease, and while it is present in about three-quarters of the cases during the second week, it may be delayed much longer, and even into convalescence. Its value is, therefore, limited at the very period in the disease in which a diagnostic test is most needed; for while it is often comparatively simple to recognize typhoid fever in its later stages, it is at the onset, during the first week, that the most doubt arises, and it is in the early days of the disease

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that the danger of contact infection is probably greatest. Moreover, there are certain atypical cases in which the reaction is never obtained. Next to the lateness of the appearance of the agglutination test, its greatest disadvantage is that it is not absolutely specific. It does not always give an etiologic diagnosis. That an agglutination of the typhoid bacillus may be produced by the serum of a patient infected with one of the paratyphoid bacilli is not of great clinical importance; but that the test may be obtained in cases in which the etiologic organism is the pneumococcus,[7] the *Bacillus proteus*,[8] or some other organism not closely allied to the typhoid group, is a fact not to be neglected. The exact percentage of error in the agglutination test it is, of course, impossible to calculate. That it is, however, a very appreciable error any one who has had occasion to use the test extensively must realize. In spite of the fact that the agglutination reaction is in itself by no means an ideal diagnostic measure, it is of the utmost value in certain cases, and especially so when taken in conjunction with the blood culture. In the early stages of the disease, before the agglutination test is positive, the diagnosis is made in most cases by the culture; and in the later stages, when the organism can no longer be isolated from the blood, the agglutination reaction is usually present. Thus the one test is supplemented by the other, and in these two comparatively simple clinical methods—the agglutination test and the blood culture in ox bile—we have the means of making an accurate diagnosis of typhoid fever, in the great majority of cases, at any stage in the course of the disease.

DISCUSSION.

Dr. R. L. Jones, Nashville, Tenn.: One of the most important additions to our knowledge of the subject of typhoid fever made in recent years is the means for an early diagnosis, which has been made practicable for us by Dr. Peabody. He will place us under still further obligation if he will make the

8. Zeit. f. klin. Medizin, 1905, p. 27.

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technic clearer. I have been engaged in this work and have had to work out some of the technic myself. Does the kind of ox bile used make any difference? I find that it is quite different when you get a steer in good condition whose bladder contains considerable bile; the bile will be of a bright green color, while that from a cow or steer not in good condition is more apt to be of a golden yellow color. Butchers tell me that this is the rule. This bright green bile if kept some time will change to the golden yellow color, and I have found that it takes the typhoid organisms longer to develop in the golden yellow bile. If Dr. Peabody uses fresh bile I would like to know how fresh; how long it will keep after sterilizing; and if there is any method by which we can keep it indefinitely in stock.

Dr. Francis W. Peabody, Boston: I can only say that we have never had any trouble at all. We have taken the bile from several different animals and used it as it came from the slaughter-house. Lately we have been using pig's bile, which seems to give as good results. As to keeping the bile after it is sterilized, we have had no difficulty on this point, and have used successfully bile that was four months old. It was sterilized as soon as it came from the slaughter house, kept in bulk in the ice chest, and put into test-tubes as it was needed.

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TYPHOID BACILLI CARRIERS.

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NEW YORK CITY.

The obscurity of the origin of a large percentage of typhoid fever outbreaks led many observers to the supposition that perhaps some saprophytic member of the colon group might change under bad hygienic conditions to the typhoid bacillus.

Further investigation revealed the fact that a small percentage of persons after recovering from typhoid fever pass typhoid bacilli in the urine. The attack of typhoid fever in some of these cases had been a number of years before. Continued examinations showed that these cases were comparatively rare, and it did not seem possible that they could account for all outbreaks of typhoid fever, where one could not trace the infection to those having the disease.

In 1902 von Drigalski and Conradi found typhoid bacilli in stools of four persons who had had no typhoid fever symptoms, but had been in contact with typhoid patients. Soon it was found that a number of typhoid convalescents continued to pass typhoid bacilli for long periods after recovery. Examinations of persons who had had typhoid fever years before revealed the remarkable fact that 1 or 2 per cent. of them were passing typhoid bacilli, sometimes in enormous numbers. The knowledge that the gall bladder had been found infected at operations for calculi suggested this as the source of the bacilli.

A number of autopsies or operations have since been held on these typhoid bacilli carriers and proven this to

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be the case. Thus, Levi and Kayser reported, in 1906, a case of a woman, 49 years old, who had had typhoid fever in 1903 and made a good recovery. In 1906 the woman died from some other disease; autopsy was held nineteen hours after death. Typhoid bacilli were present in the liver, in the wall of the gall bladder and inside a number of calculi.

Kayser reports that in Strassburg during the year 1904-5 13.5 per cent. of all cases of typhoid were traced to 6 of these typhoid carriers, all of whom were women and gave histories of having had typhoid from one to 27 years before.

A large number of cases of typhoid fever have now been traced to these chronic bacilli carriers. Thus, Lentz states, in 1905, that seven physicians had then reported typhoid cases from bacilli carriers. The first reports the case of a patient who had had typhoid 3 years before, who was known to cause 2 cases of typhoid; the second reports 4 typhoid carriers, who had had typhoid as long ago as 42 years, 15 years, 13 years and 12 years, respectively. To these 4 were traced 12 cases of typhoid. The third reports a typhoid carrier who had typhoid 19 years before, who caused 6 cases of typhoid. The fourth reports a carrier who had had typhoid 1½ years before, but to whom no cases had been traced; the fifth had a patient who had had typhoid 17 years before and had caused 27 cases; the sixth had a patient who had had typhoid 10 years before and had caused one other case, and the seventh reported a bacilli carrier who had had the disease 17 years before. To this last individual 2 cases were due.

Out of 400 recorded typhoid patients Lentz found that 6 retained the bacilli at the end of periods ranging from 3⅓ to 13 months. Klinger examined the feces of 1,700 healthy persons who had never knowingly had typhoid and found bacilli in 11.

When the bacilli were in the stools of typhoid carriers, Lentz found that he could not get rid of them by

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any treatment. Their retention is due, he thinks, to faulty metabolism and concomitant chronic disease. Faulty care during convalescence may also be a cause.

He notes the predominance of women who are carriers over men, and especially married women who have borne children.

In most cases, the bacilli are present in great numbers. Lentz suggests that the gall bladder may not be the only source, but that the appendix and the deeper folds of the intestine may also be involved.

In conclusion, he suggests the following procedures for controlling these carriers. These, as we note later, can hardly be carried out except in special cases.

1. Disinfection of stools.
2. Disinfection of privies.
3. Police notification.
4. Bacteriologic control of stools.
5. Prevention of any occupation in which the carrier is in a position to infect others.

INVESTIGATIONS ON TYPHOID CARRIERS AT THE RESEARCH LABORATORY DEPARTMENT OF HEALTH.

History.—On March 20, 1907, a cook was brought to the laboratory to have the feces and urine examined. The history as developed by Soper revealed the fact that during the past eight years she had been employed in eight families and in seven of these typhoid fever had broken out within a few weeks or months of her arrival. In all twenty-six cases and one death occurred. Just before her removal to the Department of Health two cases had developed in the family where she resided and one patient died. Bacteriologic examination revealed the fact that fully 30 per cent. of all the bacteria voided with the feces were typhoid bacilli. The urine was negative. Careful cultural and agglutination tests showed that they differed in no respect from bacilli obtained from acute cases. The repeated outbreaks occurring after her entrance in families were in themselves proof that the virulence of the bacilli had remained intact. A curious feature of the case is that the woman denies that she ever had typhoid fever.

Treatment.—This woman has now been isolated for sixteen months. Weekly examinations of the stools have usually

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revealed large numbers of bacilli, but there have been several intervals when for one or two weeks no bacilli could be detected. Treatment by intestinal antiseptics has proved unavailing. Hexamethylenamin in doses gradually increasing from 100 up to 150 grains a day, has been given for a number of weeks with no apparent benefit. Attention to diet and mild laxatives has caused the greatest reduction, but not their disappearance. This suggests that the chief development of the bacilli is in the intestines, although the source of the infection is probably the gall bladder.

The case of this woman brings up many interesting problems. Has the city a right to deprive her of her liberty for perhaps her whole life? The alternative is to turn loose on the public a woman who is known to have infected at least twenty-eight persons.

This case excited so much interest that I decided to have tested a large number of typhoid convalescents. Eight months ago there was a typhoid epidemic at the Trenton (N. J.) State Insane Asylum. Through the courtesy of those in charge we were able during the past two months to examine the stools from 52 persons who had had typhoid at that time; 2 of these were found to pass numerous typical typhoid bacilli. Their stools were examined four times. One case revealed the bacilli only once, in the other they were present every time.

The stools of 16 persons, who had suffered from typhoid fever in the Long Island State Asylum, were sent us by Dr. Agnew. Two of these persons were found to pass abundant typical typhoid bacilli; they had been well for six months. Repeated examinations have shown the constant presence of bacilli. One of these cases was so mild that the patient was only suspected to have typhoid fever because of the other cases of that disease.

We have, therefore, found typhoid bacilli in the stools of 6 per cent. of the cases examined. During the autumn we examined the feces from a large number of persons convalescent from typhoid fever just as they

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left the hospital and found bacilli persisted in the feces of about 5 per cent. It was impossible to trace the cases further.

The bacteriologic tests were carried out by Dr. Goodwin and the Misses Noble and Pratt, bacteriologists in the Research Laboratory.

These examinations indicate that the same conditions exist in this country as in Europe, namely, that fully 2 per cent. of persons who have had typhoid fever are typhoid bacilli carriers. A few of these pass infected urine, but most infected feces. Besides these there are numerous typhoid carriers who never had typhoid fever, but through contact with infection became bacilli carriers. Probably at least one in every five hundred adults who have never knowingly had typhoid fever is a typhoid bacilli carrier.

As the majority of typhoid cases occur before the age of 30, the average life of typhoid carriers is fully 25 years, so that we have the somewhat appalling fact that there are at least half as many recovered typhoid cases who are typhoid carriers as there are typhoid cases in any year and that, besides these, there are the typhoid carriers, such as the cook, who have never had typhoid fever.

What can we do under these circumstances? It seems to me that any attempt to isolate and treat on bacteriologic examinations, as Lentz suggests, is impracticable. When we consider that the presence of the bacilli in the feces of these persons is often only occasional, that numerous contact cases having never had typhoid fever would not come under suspicion, and finally, the impracticability of isolating for life so many persons, we are forced to consider isolation utterly impracticable, except as in the case of the cook already described, where conditions increase the danger to such a point that an attempt at some direct prevention becomes an essential.

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We must, therefore, as before, turn to the more general methods of preventing infection, such as safeguarding our food and water, not only chiefly when typhoid fever is present, but at all times, for we now know that in every community, whether it be large or small, unsuspected typhoid bacilli carriers may always be present.

DISCUSSION.

DR. HENRY ALBERT, Iowa City, Iowa: A small epidemic of typhoid fever, traceable to a bacillus carrier, occurred in Cedar Falls, Iowa, last fall. It was an epidemic of thirteen cases of typhoid, occurring at about the same time in three families that lived in the same neighborhood. The water supply was first investigated and it was found that these families were using the ordinary supply of the city, the same as that used by a majority of the people. The water supply as the medium of infection having been ruled out, the milk supply was next investigated and it was found that the families in which the cases of typhoid occurred all obtained their milk from one source, and that no other family in the city was supplied from this source. We then investigated more in detail as to the possibility of the contamination of the milk and found that the owner of the cow, who also did the milking, had had typhoid about fifteen months previously, but had not had a sign or symptom of typhoid since, or for more than a year. A bacteriologic examination of the urine and feces of this man was made and typhoid bacilli found in the urine in considerable number. There was no evidence of an inflammatory condition of the kidneys or bladder. We felt reasonably certain that the epidemic was caused by this bacillus carrier. Hexamethylenamin in the form of urotropin was given and in a few weeks the urine was free from the typhoid bacilli. I feel certain that other epidemics I have observed in the past were caused by individuals of this kind.

DR. WILLIAM LITTERER, Nashville, Tenn.: The subject of typhoid carriers is an exceedingly important one. I have in mind a patient who had typhoid fever one year ago. The patient subsequently developed a post-typhoid necrosis of the rib which was operated on by Dr. W. A. Bryan of Nashville. A sinus appeared and a large amount of pus exuded from this wound, something like four or five ounces a day. This condition existed for three months, the patient growing weaker, rapidly losing flesh, and vague pains developed throughout the body. The surgeon requested that I isolate the organisms in said pus and make a vaccine according to the method of Wright. This I did and much to my surprise I found pure culture of the *Bacillus typhosus* in enormous numbers. I take this to be unique inasmuch as no other organism, such as the

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pyogenic cocci or other bacteria could be found in this exuding sinus of over three months' standing. I made a comparative estimate of the number of typhoid bacilli in this pus and found that an ordinary platinum loop full contained nearly a half million of bacilli. This case could be rightfully considered as one of a typical typhoid carrier and an especially dangerous one if the discharges from the sinus were not destroyed. Two months' injection with the autogenous typhoid vaccine produced very gratifying results. The patient is much stronger, gaining steadily in weight and there is an absence of the vague pains throughout body. The sinus has almost healed, only about half a dram of pus exuding in the twenty-four hours. Recently I made another bacteriologic examination and found only a few typhoid bacilli and some specimens of *Staphylococcus pyogenes aureus*. If the patient ceases to improve I intend to make a staphylococcic vaccine and inject this, with the typhoid vaccine. Dr. Park has called attention to the fact that many of these "carriers" have an infected gall bladder, and it has been suggested by some that, in order to cure this condition, a surgical operation would be necessary. It might be possible to try vaccine therapy in curing these conditions.

Dr. M. J. Rosenau, Washington, D. C.: I can not take Dr. Park's place, but feel sure that if he were here he would say that "typhoid Mary" refuses to submit to surgical interference. She is perhaps justified in this conclusion, because the gall bladder is not the only source of the typhoid bacilli that appear in the feces. Surgical interference therefore may not always correct the condition. Sometimes the feces of these carriers contain such large numbers of typhoid bacilli as almost to displace the colon bacillus; it seems that the typhoid bacillus may take up a natural habitat somewhere in the intestinal tract indepedendent of the gall bladder. We have not been able to find a chronic bacillus carrier of this type in Washington.

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METABOLISM IN TYPHOID FEVER.

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I shall not attempt to review the many-sided subject of metabolism in typhoid fever, but shall devote the time to a brief discussion of one phase of the subject, which is of great importance, as well as of interest, both to the clinician and to the pathologic physiologist.

During the course of the disease a typhoid patient loses from ten to sixty pounds, or even more, of his body tissue. This loss is divided among water, subcutaneous fat and protein from the body fluids or cells. The loss of water we may leave out of consideration because we know neither its amount or significance. Since the observation of Leyden[1] in 1869 it has been believed that there is a retention rather than a loss of water from the body in fever. This belief is supported by the decreased quantity of urine and by the supposed decrease in the evaporation from the skin; but few or no accurate data on this question are available, and no positive statements concerning it can be made.

The burning of body fat may, in the absence of carbohydrates, and perhaps also other conditions, lead to varying degrees of acidosis, with an abstraction of alkalis from the tissues, and possibly in other ways may be of distinct harm to the patient. This is borne out by the clinical observation that fat individuals are comparatively poor subjects for typhoid fever, or for

1. Arch. f. klin. Med., 1869, v, 366.

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that matter, for any infectious fever or for surgical operations. We have, however, as yet no good reason for believing that the metabolism of fat in fever is in any way different qualitatively from that in other conditions of undernutrition; and it seems to me probable that the excretion of the acetone bodies occasionally recorded in typhoid fever is merely the result of a burning of body fat in the absence of sufficient carbohydrates—the frequently observed starvation acidosis. If this is true, acetone, diacetic and beta-oxybutyric acids will not be excreted by the typhoid patient who receives an abundance of carbohydrates. Aside from the production of organic acids in the burning of body fats, the mere loss of fat is probably of no great consequence.

In addition to the loss of body fat there is a great loss of body protein in typhoid fever, and this is what I shall speak of in some detail. Many data are to be found in the literature as examples of the amount of this loss of protein. In a case reported by Leyden and Klemperer[2] there was a loss of 109 gm. of nitrogen, the equivalent of 3.2 kilos or seven pounds of pure muscle tissue in twelve days. In a case of Frederick Müller[3] there was a loss of 86.4 gm. of nitrogen, the equivalent of 2.5 kilos or five and one-half pounds of muscle tissue in eight days. These are not very unusual figures; a loss of the equivalent of even one and one-half pounds of muscle tissue in a single day is not very rare. There are many reasons for believing that this febrile loss of protein from the body is a serious and dangerous proceeding. The emaciation, muscular weakness and decreased resistance, and the long convalescence are certainly in part the results of the loss of body protein. The amount of protein lost appears to bear a close relation to the severity of the disease, and Ewing believes that the pathologic processes concerned in the metabol-

2. Von Leyden: Handbuch der Ernährungstherapie, 1904, ii.
3. Cong. f. inn. Med., 1902, p. 192.

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ism of this body protein take a prominent part in determining the patient's condition. Ewing's[4] idea is that many of the phenomena of typhoid fever, especially in the severe and fatal cases, are due to an autointoxication resulting from the "burning of thirty pounds of body tissue in three weeks"—and not directly to the endotoxins of typhoid bacilli. This idea is to some extent supported by the fact that the so-called nitrogen partition of the urine in severe or fatal cases is decidedly abnormal, and similar to those found by Wolf, Ewing and others in toxemia of pregnancy. Furthermore there are severe so-called toxic cases of typhoid fever which terminate with acute yellow atrophy of the liver, a condition which appears to be closely associated with a particular type of faulty protein metabolism. But aside from the possibility of its creating an autointoxication, the consumption and loss of body protein must be of great harm to the patient, both during the disease and during convalescence.

The causes for this loss of body protein are apparently three in number.

The first is partial starvation. An individual is obviously undernourished unless he absorbs from the digestive tract food of sufficient caloric value to equal the energy expended. Except by very difficult and accurate measurements it is impossible to know the amount of energy being expended by a particular patient, and few such measurements have been made on fever patients; but we may readily calculate average figures which are satisfactory for practical purposes.

At ordinary rest the heat and other energy expended by a normal individual receiving sufficient food is about thirty-three calories per kilo body weight. In fever there is an increased heat production, with an average, according to Krehl, of 20 to 30 per cent. Twenty-five

4. Proc. Path. Soc. Philadelphia, 1905: paper before New York Acad. Med., New York Med. Rec., 1907, p. 537.

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per cent. added to the thirty-three calories gives about forty calories, or, for a patient weighing seventy kilograms, or 150 pounds, 2,800 calories. This represents the minimum amount of energy which the average typhoid patient is expending in each twenty-four hours. If he does not receive food equivalent to this amount of energy he merely draws on his body tissues to make up for the deficit. Few or no typhoid patients receive enough food to maintain an equilibrium, and they consequently burn up for fuel varying amounts of their body fat and protein.

Any physician can readily calculate the probable deficit with the diets he uses. The deficit in calories is usually about 50 per cent., and this, according to von Noorden's figures,[5] may be responsible for loss of 2 to 3 gm. of body nitrogen per day.

The two other causes for the febrile loss of body protein are the pyrexia and the action of the bacterial toxins. From the experiments of Linser and Schmidt,[6] Fritz Voit[7] and Schleich,[8] we know that artificially raising the body temperature causes an increase in protein metabolism. The pyrexia itself is therefore one of the causes for the loss of body protein; but the loss due to this cause can be prevented, just as the loss due to partial starvation, by the intake of sufficient food.

The third factor is the so-called "toxic" destruction of body protein from the poisonous action of the bacterial toxins on the body protein. This last factor is still open to discussion, but I am inclined to the belief that some such action does take part. It is, however, at present impossible to discuss the toxic destruction apart from the result of the pyrexia, because we can not distinguish between the two when both are present, as they usually are in typhoid. The question which is of im-

5. Handbuch der Pathologie des Stoffwechsels, 1906, i, 497.
6. Arch. f. klin. Med., lxxix, 514.
7. Sitzungsb. d. Gesellsch. f. Morphol. u. Physiol. in München, 1895, No. 2.
8. Arch. f. exp. Pathol. u. Pharmakol., iv, 82.

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portance for the practical treatment of typhoid is, can the combined effect of the pyrexia and the bacterial toxins be prevented from causing a loss of body-protein? There are already some encouraging answers to this question. May,[9] working with rabbits infected with pig erysipelas, was able to decrease the febrile loss of body protein by carbohydrates; though May later doubted the correctness of his first interpretation. Puritz[10] worked on human typhoid in St. Petersburg, and his results led him to favor a liberal diet in this disease. His diets, however, were rich in protein and of only moderate caloric value, and were therefore, I believe, not well adapted for his purpose, which was to retard the loss of protein. Weber,[11] working with a sheep inoculated with an extract of glanders bacilli, was able wholly to prevent any febrile loss of body protein by giving the animal a liberal diet containing much carbohydrate. Leyden and Klemperer, on the other hand, conclude from their experiments on typhoid and pneumonia that, while a liberal diet is desirable, it is not possible to prevent the febrile loss of protein; this view is generally accepted.

Last summer Dr. Warren Coleman and I undertook in Bellevue Hospital, New York, a further study of the extent to which the loss of body protein in typhoid fever might be retarded by dietetic means.[12] Our results were on the whole very encouraging, in that we were able to diminish the loss of body nitrogen to a comparatively small amount during the fastigial temperature and were able to make patients gain body protein during the steep curve period of the disease.

I need not here go fully into the reasons underlying our choice of diet, which is the opposite of that used by Puritz, and indeed the opposite, in some particulars, of

9. Ztschr. f. Biol., 1894, xxx, 1.
10. Virchows Arch. f. Path. Anat., 1893, cxxxi, 327.
11. Arch. f. exper. Path., xlvii, 10.
12. We are indebted to Dr. Armstrong, medical superintendent of Bellevue Hospital, for placing the facilities of the hospital at our disposal. The experiments will be published elsewhere in detail.

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the diets at present used in typhoid fever by most physicians. Our principle has been to have the diet contain a moderate amount of protein and the largest possible amount of carbohydrate. The reasons for choosing carbohydrates as the basis of the diets were briefly as follows: Carbohydrates are the strongest sparers of body protein in health, according to Voit, Lusk, Folin and others; and the experiments of May, Weber and Linser and Schmidt indicate that this sparing action takes place in fever as it does in health.

TABLE OF COMPOSITION OF FOOD DURING EXPERIMENT SHOWN IN CHART.

The numbers at the left refer to corresponding numbers on the "nitrogen balance" curve in chart.

		Gm.	Calories.	Per Cent. Total Calories.	Calories Per Kg. Body Wt.
1.	Protein	60	245	7.8	
	Fat	80	745	23.7	
	Carbohydrate	525	2150	68.5	
			3140		58.
2.	Protein	56	230	6.2	
	Fat	78	725	19.5	
	Carbohydrate	670	2750	74.3	
			3705		69.
3.	Protein	53	217	8.7	
	Fat	63	585	23.6	
	Carbohydrate	410	1680	67.7	
			2482		46.
4.	Protein	75.5	310	8.2	
	Fat	120.4	1120	29.8	
	Carbohydrate	569	2330	62.0	
			3760		70.
5.	Protein	16.2	66	2.0	
	Fat	108	1004	30.3	
	Carbohydrate	547	2240	67.7	
			3310		62.
6.	Protein	84	345	20.0	
	Fat	96	893	51.7	
	Carbohydrate	120	490	28.3	
			1728		32.
7.	Protein	85	349	8.8	
	Fat	122	1234	28.7	
	Carbohydrate	583	2390	62.5	
	Alcohol		80		
			3953		73.

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A large amount of fat is objectionable because of its tendency toward digestive disturbances and diarrhea; and the protein should be kept at the minimum effective amount because of its action in increasing the heat production (Rubner) and because of the large amount of work it throws on the intestine and the kidneys. The results from one of our cases are given in the accompanying chart. Samples of the diets used are given in the table.

Our results with other cases show essentially the same thing, although in some cases there was no gain, but a continued slight loss of one gram or so per day. On the high caloric diets, however, the patients were almost always in a condition not far from nitrogen equilibrium.

Our results show, we believe, that the febrile loss of body protein, including the result of the three factors, undernutrition, pyrexia and the action of toxins, may be retarded and even wholly prevented, or compensated for. But the results show likewise how difficult this is to accomplish. It was only when we gave sixty to seventy or even eighty calories per kilogram—between 3,000 and 4,000 calories—that the greatest sparing was observed.

The important point is, however, that it is possible to give typhoid patients such liberal diets without, so far as our experience shows, producing any harmful results, but, we believe, with decided benefit.

Having learned that it is possible to retard the febrile loss of body protein, we have still to decide whether it is desirable to do so in typhoid fever.

There are many objections, some apparent and others real, and many formidable difficulties; but I know of no reason why we should not attempt to do all in this direction that the circumstances will allow. Among the possible objections to liberal feeding in typhoid is the commonly supposed digestive limitation of these patients. The digestion in typhoid fever undoubtedly has

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its limitations, but they are not such as to prevent the proper absorbtion of amply sufficient food if given in the proper form. The experiments of von Hoesslin,[13] Leyden and Klemperer,[12] Puritz,[10] Folin[14] and others show very positively that the average typhoid patient absorbs food from his intestine almost as completely as does the healthy individual. Only in the severest cases is the absorption very materially decreased. In the average case without profuse diarrhea the digestion of protein, fat and carbohydrate is within 10 or 15 per cent. of the normal. Folin,[14] in his recent work on typhoid, has directly determined the degree of absorption of carbohydrates and has found it practically normal.

What seems to me an objection to liberal feeding in typhoid fever is the effect of the protein in increasing the heat production. Rubner[15] has shown how a strict protein diet in a dog may increase the heat production more than 50 per cent. The effect in a human patient could never be so great, but with the decreased heat loss in fever it is quite possible that this factor may be of considerable importance. This objection does not hold against the diets Coleman and I have used, but may apply to the high protein diets used by others. Carbohydrates have only a very slight effect in increasing heat production.

The objection has been raised to the use of large quantities of carbohydrates, from the fear of fermentation and tympanites. I can only say that we have had no such experiences with the use of milk sugar or starch.

The greatest practical difficulty that we have so far encountered in this work is the choice of food products. After trying or considering various carbohydrates we have used milk sugar almost wholly. This has the advantage of fermenting only with difficulty and of be-

13. Virchows Arch. f. Path. Anat., 1882, lxxxix, 317.
14. Unpublished experiments.
15. Rubner: Die Gesetze des Energieverbrauchs, 1902.

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ing less sweet than cane sugar and much more soluble than any form of starch. Milk, diluted cream, and eggs have been used to furnish protein and fat. Cocoa, lemon juice, tea, coffee and other things have been used as flavoring agents and as vehicles for milk sugar.

The patients did not object to our diets more than to milk alone, but some persuasion was frequently necessary to get them to take the amounts of food found to be necessary for our purposes.

The full advantages as well as the possible objections to our dietetic plan have still to be demonstrated; but there are a few reasons in favor of such liberal nourishment for typhoid patients which are worthy of consideration at this time.

As I pointed out earlier, the average typhoid patient receives at present 50 per cent. or less of his energy requirement. This is half starvation; and we know that starvation is harmful even in health, in that it leads to weakness and to an increased susceptibility to many infectious diseases. If starvation is harmful in health why should it be beneficial in typhoid fever? During the course of typhoid fever great demands are constantly being made on the defensive power of the organism; and it certainly does not seem probable that the patient will be as well prepared to meet those demands when in a starved or half-starved conditions as when he is being supplied with sufficient energy in the form of food.

It is a common laboratory observation that strong, robust, well-fed animals develop the strongest artificial immunity; and it seems fair to believe that we are assisting the patient to acquire his immunity to typhoid fever by keeping his nutrition at the highest possible level. Is it not possible that one of the factors determining the outcome of the disease may be the state of nutrition in which the body cells are maintained? Retarding the loss of body protein should leave the patient at the end of the fever in better physical condition and so make possible a shorter convalescence.

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This sort of reasoning is, however, largely speculative; and long experience alone can tell the true value of such treatment. We can merely say at present that it is possible by the means already outlined to retard and even to prevent the febrile loss of body protein.

414 East Twenty-sixth Street.

DISCUSSION.

DR. LAWRENCE LITCHFIELD, Pittsburg: During last summer I spent a great deal of time reading all I could find in the Surgeon General's Library on metabolism in typhoid, and from the crude experiments of Leyden, published in 1869, attempts made by increased feeding to prevent or control the loss of weight during the course of the fever, through the work of von Hösslin, whose classic article was published in 1882, and the excellent work of von Leyden, Klemperer and others down to that of Lüthje, who published in 1902 the report of his successful attempts to establish a plus nitrogen balance during the period of steep curve, though with very high proteid feeding, this work of Drs. Shaffer and Coleman is unquestionably the best that has been done on the metabolism of typhoid up to the present time.

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THE TREATMENT OF TYPHOID FEVER.

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There is no intention in this paper to endeavor to discuss all the phases of the treatment of typhoid fever, but those will be considered about which there is the greatest difference of opinion or which deserve special emphasis. In the consideration of the handling of a patient with typhoid fever we must always have the individual in mind and care for him rather than treat a disease. No one method suits every patient any more than clothing made to one measurement fits every man. The man can exist whether the clothing suits his figure or not, but he is not garbed to the best advantage. In the same way one method of treatment may bring a certain patient through the illness, but not in the easiest or best way. It seems to me that the importance of drilling this fact into our students should be more realized by those of us who are teaching therapeutics—and every clinical teacher must consciously or unconsciously be teaching something about the care of the patient—for there would be less of rule-of-thumb methods if individuality in treatment was the rule in the minds of each one of us.

DIET.

Much controversy has been waged over diet. Most of us have our own ideas and are not easily convinced that any others can be better. No matter what views

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are advanced some one will disagree vigorously, which is by no means a disadvantage. This divergence of opinion is not surprising when we consider what a protean disease this is and as much so in the ways in which it is handled as in its manifestations. Many patients will go through an ordinary mild attack with any reasonable kind of food, but I feel that in the attack of ordinary severity and in all severe attacks, the simpler the diet the better for the patient. Milk and albumin water are satisfactory, easily obtained and prepared, and cheap. We should always be careful to make certain that we are not giving contaminated milk. For the account of a good object-lesson as to the importance of this precaution a paper by Edsall[1] may be consulted. To these may be added the various modifications of milk, of which whey is specially useful, bouillon, strained gruel, ice cream, tea and coffee, and sometimes cocoa; this list really gives considerable choice. Emphasis should be laid on the value of whey in the dietary. In the conditions in which milk disagrees whey may be given with great advantage. The importance of carefully watching the stools and being guided by them as to changes in the diet should be remembered. In all cases special emphasis should be laid on the giving of large amounts of water. Let one hundred ounces (3,000 c.c.) of urine a day be the minimum to be desired, and often it is better that larger amounts than this should be passed. Consider the experience of the Lakeside Hospital in Cleveland,[2] where it was found to be a saving in the time of the nurses to have one nurse especially detailed to do nothing else than give water to the typhoid fever patients. There does not seem any evidence for the opinion held in some quarters that there is the possibility of harming the kidneys. The work of Sollmann and Hofmann[3] speaks against this. The void-

1. New York Med. Jour., 1905, lxxxi, 578.
2. Cushing and Clarke: Am. Jour. Med. Sc., 1905, cxxix, 187.
3. Am. Jour. Med. Sc., 1905, cxxix, 195.

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ing of large quantities of urine does not seem to cause the patients any disturbance. There does not seem to be any danger of giving the circulation too much work to do in handling this fluid. One should use judgment if the myocardium is weak, but in a large series of cases no evidence of overloading of the heart was found.

There are certain intestinal conditions in which there seems no question of the advantage of the simple diet. These are especially meteorism and perforation. With any tendency to tympanites, it is wise to give the simplest diet and not too much of it; when tympanites is present the diet should be reduced. Therefore, does it not seem that on the simple diet there is less chance of its appearance? I am of the opinion that liquid diet and large amounts of water are the surest preventives of meteorism. Certainly when this treatment is carried out the occurrence of meteorism is reduced to a minimum, and the best treatment of meteorism is its prevention. If perforation occurs and operation is done early, it is a great disadvantage to have the intestines distended or full of material. We can count on a certain percentage of perforations in any large series of cases, but we can not tell at the outset which ones are to perforate.

Under the heading of diet reference must be made to the so-called predigested foods, which are so extensively used. Is their use justified or to be recommended? Many of the profession by their actions answer in the affirmative and the question comes as to how much justification there is for this belief. I would advise all those who have any doubts on this subject and those who believe in the value of these foods to read with an open mind the report[4] of the Council of Pharmacy and Chemistry of the American Medical Association on them. The main objections to their use may be thus summed up:

4. The Jour. A. M. A., 1907, xlviii, 1612.

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1. They contain comparatively little nutriment.

2. They may be directly injurious from the presence of peptones or albumoses, which are of uncertain composition and may be toxic or become so.

3. The presence of alcohol in them may be harmful.

4. They are expensive.

Clinically they certainly appear in some cases to upset the stomach and cause diarrhea and distention. To give amounts of these foods which would go even a small way toward nourishing the patient, means the administration of considerable amounts of alcohol. If alcohol is to be given, it is better to give it as such and not as the constituent of one of these foods.

That any one who knows their composition can persist in considering that they have some mysterious nutritive virtue is hard to believe; and yet how else can we explain the blind belief in their value, especially when we consider that they are "drug-store" foods and may have had some time to "ripen" before being used? Their cost is a serious objection, especially when so little is obtained in return.

CARE OF THE BOWELS.

An initial purge is advised by many authorities; but is anything gained by it? It is asserted that there is an advantage in emptying the bowels. The patients who are not purged seem to do just as well—in fact, better. A study which I made of five hundred cases, in which this point was specially noted, showed that diarrhea, not only at the onset, but during the course, occurred in a much larger number of those who were given an initial purge than in those whose bowels were left alone. If the patient's intestinal tract is not disturbed and a simple diet with much water given, it is surprising how infrequently diarrhea occurs.

Constipation is to be preferred and as a rule a movement every second day is often enough. If the bowels do not move themselves an enema may be given. This

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may be the ordinary one of soap and water, or oil and glycerin may be given. It is sometimes well to give an oil enema high in the bowel through a long tube, which, if necessary, may be followed by a simple enema. The comfort of the patient must be consulted; some patients are easier if the bowels are moved every day.

THE USE OF OPIUM.

In the majority of indications usually given for the use of opium I would oppose the views laid down in many of the books. The conditions for which it is generally employed are: First, restlessness and sleeplessness; second, diarrhea; third, hemorrhage, and fourth, abdominal pain.

1. *Restlessness and Insomnia.*—Here in small doses its use is sometimes advisable, but if indicated it often seems better to give small doses of morphin hypodermically.

2. *Diarrhea.*—Here, as is usually the case in diarrhea in general, opium should be the last drug to be used, instead of the first, as is too often the case. The cause should be searched for first, for too often this is left to act and opium is given to prevent the result. An initial purge, improper feeding, the giving of beef tea or predigested foods, the use of infected milk—any of these may be the cause. The diet should be cut down to albumin water, or if milk is given it should be boiled, and sedatives, such as bismuth, may be given. If opium is needed it should be given as the starch and laudanum enema. Given by mouth, opium favors distention and conceals the most valuable symptom of perforation, abdominal pain.

3. *Hemorrhage.*—Here the standard treatment is to give opium, especially in the form of the lead and opium pill. To this treatment, although sanctioned by tradition and authority, I would take exception. The advantage is claimed for it that peristalsis is lessened. Have we any proof that this is an advantage? It may

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lessen the chance of a clot being dislodged, but when we think how rarely a clot is found at autopsy in patients who have died after hemorrhage, the importance of this does not seem great. Against the use of opium there are several points. It increases the chances of distention, in itself a serious matter. In the case of gastric ulcer, distention increases the chance of perforation and the same is probably true of the bowels. Then in a considerable number of cases hemorrhage and perforation occur together. Give opium for the hemorrhage and we know the end. It comes painlessly, but surely. Any one who has been called in consultation to decide as to the possibility of perforation in a patient who has had large doses of opium, knows how hopeless it is to give any opinion. Then, too, the giving of large amounts of opium seems to have an injurious effect on the general condition of the patient.

4. *Abdominal Pain.*—Under no circumstances should opium be given, for this is our chief aid in the recognition of perforation. The men who treat many patients with typhoid fever and say that they never have perforation probably do one of two things, perhaps both (possibly it would be better to say they do one and leave the other undone); they give opium or do not have autopsies.

The first thing in the treatment of abdominal pain is to determine the cause. Evidently if it be due to a distended bladder, meteorism or impacted feces, we are not going to help matters, but rather make them worse, by giving opium. If the cause can be found the indications are clear; if it can not be found we must not give a drug which prevents our determining the cause, certainly in the more serious conditions. When the cause is not determined—and these cases are not very rare—simple measures, such as the application of stupes or small doses of bromid of potassium or codein may be enough. If the pain is not relieved by these, it

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may be necessary to give a small dose of morphin hypodermically (gr. 1/8), which is always to be preferred to opium. In this dosage it is not likely to mask abdominal symptoms.

HEMORRHAGE.

There seems no doubt that the use of the calcium salts, preferably the lactate, is helpful. In hospitals, or elsewhere when possible, it is well to take the coagulation time of the blood when the patient comes under observation. If this be prolonged it is well to give the calcium lactate as a prophylactic measure. Too large doses should not be given; probably twenty grains a day is enough. In case of hemorrhage the drug should be begun at once and thirty grains a day may be given. When it is important to obtain a rapid action the calcium lactate may be given subcutaneously in a 1 per cent. solution. The use of astringent drugs, such as lead acetate, or the giving of ergot, does not seem to be of any use and the latter is perhaps harmful. Quiet is essential and if the patient is restless this may be secured by a small dose of morphin (gr. 1/8) hypodermically. it is well to limit the amount of food by mouth, reducing the diet to albumin water or sometimes to water alone.

To keep the patient quiet, to limit the intake, to apply a light ice-bag to the abdomen, to give the calcium salts, not to give opium, and not to try to do too much, seem the main points in the treatment of this complication, which after all is not usually as dangerous as has been thought.

PERFORATION.

How many of the five thousand[5] patients every year in the United States in whom perforation occurs are saved and how many should be saved? If those two figures do not correspond, where is the blame? To de-

5. This is, of course, only a general figure. The actual number is probably much greater.

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termine how many should be saved is difficult, but it is a question whether we are sufficiently awake to the frequency of perforation, or to the importance of its early recognition and treatment. There is no doubt of the much greater difficulty in diagnosis and treatment when patients are treated at their homes than when they are in a hospital. Still, even here it would seem that much more might be done. To make an early diagnosis of perforation, preparations must be made beforehand. As a rule the diagnosis does not force itself on the careless observer. The lesson of the importance of prompt cooperation between the medical and surgical sides has been learned in many hospitals, but there are still some in which more attention might be given to this. The early recognition of this complication is as much a matter of treatment as anything else.

DISTENTION OF THE STOMACH.

While we are all aware of distention of the intestines, it is not so generally recognized that distention of the stomach is by no means rare. It may give considerable distress and affect both the respiration and the action of the heart. The passage of a stomach-tube gives immediate relief and no hesitation need be felt in doing it. The tube can be passed without raising the patient's head. It is well to cut down the diet to albumin water and to repeat the passage of the stomach-tube as often as necessary.

ALCOHOL.

The indications for the use of alcohol are much disputed and some of our extreme friends hold that its use is never justified. Certainly its routine use is not to be advised. I consider that the best indication for its use is toxemia. In some way or other the toxic patient can use alcohol, whether we consider it a stimulant or a food. When it is being given care should be taken to use a good variety, just as we make sure that the milk is

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good. The amount must be decided by the needs of the patient. Generally, when it is indicated, good doses are advisable, from six to twelve ounces in the twenty-four hours; two or three ounces in the same period are usually not enough. The statement is still repeated at times that the patient who is being given tub baths needs alcohol. This is by no means the case—quite the contrary. The patient who is receiving the tub treatment, as a rule, requires less alcohol, as toxemia is so much diminished. Alcohol does not require to be given merely because the patient is having baths.

HEXAMETHYLENAMIN.

When we remember the frequency of bacilluria and the very common presence of typhoid bacilli in the gall bladder, it seems wise to suggest the administration of hexamethylenamin (urotropin) to every patient. The work of S. J. Crowe,[6] who has shown that when this drug is given in sufficiently large amounts (75 gr. per diem) it appears in the bile in quantities sufficient to have a bactericidal action, proves the value of this. He also found that hexamethylenamin was present in the cerebrospinal fluid, synovial fluid, saliva, pleural effusion and blood. How much "killing out" of typhoid bacilli we can do by this means is as yet undetermined, but certainly these findings are suggestive.

The question arises as to the safety of giving such an amount of this drug (75 gr. per diem) to patients as a routine. There are reported instances[7] of hematuria following its administration. These are comparatively few, but further observations are necessary before positive statements can be made. With the number of patients of all kinds who are taking this drug it should not be long before we have definite statistics from a large number of observations. Painful micturition

6. Johns Hopkins Hosp. Bull., 1908, xix, 109.
7. Coleman: Med. News, New York, 1903, lxxxiii, 393.

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sometimes occurs, but it is not serious and disappears rapidly after stopping the drug.

Certainly in view of the fact that smaller doses (gr. 30 to 40 per diem) apparently prevent bacilluria, we should not hesitate to give these to every patient.

SEROTHERAPY.

It does not seem possible at the present time to speak with certainty as to the value of any of the various serums which have been used. The results claimed by Chantemesse are excellent, but have not been sufficiently verified by other observers.

PREVENTIVE INOCULATION.

While this has proved of some value in military medicine, especially when troops were to be sent to infected localities, yet the results have not been strikingly successful. That it can be of much value in ordinary practice seems doubtful, especially when we remember that it is not wise to employ it during the time of an epidemic, owing to the temporary increase in susceptibility following the inoculation. The "man in the street" is not likely to be willing to undergo it at other times.

THE PREVENTION OF INFECTION.

It is to this that we must devote more care than we have in the past. We quite understand what a man means if he says that he has attended ten patients who were seriously ill and brought them all through safely. But if he announced that he had attended ten patients without a single case of infection from them and no danger of infection in the future, we should wonder at first what he meant. Yet the second statement means more to the community and represents a great deal more thorough and commendable treatment than the first. It often requires care and brains and hard work to pull a patient through the attack, but it needs more of all three to ensure that he does not pass his infection on to some one else.

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The work of recent years has brought to our notice certain methods of transmission which may be emphasized. One is the importance of contact infection. How much this means through the country may be guessed at perhaps by the number of cases which occur in our hospitals. "Accidents occur in the best-regulated families," but altogether too many "accidents" of this kind occur in our best-regulated hospitals. In reference to this point, an excellent study is that by D. L. Edsall,[8] which should be read by all those interested in the subject. The report of the Commission for the Study of Typhoid Fever in the Spanish-American War (Reed, Vaughan and Shakespeare), did much to bring out the importance of contact infection.

Another method is what may be termed intermediate contact, in which the bacilli are carried by flies. How difficult this is to prevent perhaps the country practitioner can tell better than his city confrère. Unfortunately we all know it. Then there are the so-called "carriers," who go about with a supply of typhoid bacilli which are being constantly distributed.

HOSPITAL TREATMENT.

When we turn to the question of the prevention of infection and the carrying out of the proper measures, we realize the tremendous difficulties involved. Until recently the custom in Britain of sending patients with typhoid fever to special hospitals seemed rather unnecessary, but we have learned how wise such a plan is. There seems no question of the necessity of our introducing very much greater care and more stringent regulations in handling the patient with typhoid fever.

In view of the constant occurrence of instances of infection in hospitals the need of greater care requires no emphasis. The other patients, nurses, orderlies and physicians are all exposed to this risk. Precautions

8. Am. Jour. Med. Sc., 1908, cxxxv, 469.

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which we should endeavor to carry out are discussed under various headings.

a. Isolation.—Should a typhoid patient be isolated in a special ward? Undoubtedly whenever possible this measure should be carried out. In many hospitals in the ordinary incidence of the disease it seems almost impossible; there is neither the ward accommodation nor a sufficient number of nurses to carry it out. Yet we should endeavor to do it as far as possible. The typhoid fever patients should be kept together in one part of a large ward or as far as possible in one part of the hospital. Every effort should be made to have special nurses and orderlies waiting on these patients alone. The question of a separate kitchen and food supply is also important. The diet for the typhoid patients is so simple and the dishes they require are so few that it is not a difficult matter to keep these separate. One rule should be absolutely enforced—the nurses and orderlies who are waiting on the typhoid-fever patients should have nothing to do with the preparation of the food for the other patients. Too often a nurse goes directly from waiting on a patient with typhoid fever to prepare food for the other patients in the ward, or an orderly may be handling the ice for the water-cooler.

b. Physicians.—It should not be necessary to point out the necessity for care on their part, both for their own sakes and for that of the patients. It requires constant attention always to remember to wash the hands after examining a patient with typhoid fever before going on to a patient with another disease, and yet undoubtedly there is the risk of infection if this is not done. For both physicians and medical students the need of care in the examination of the urine and stools from typhoid fever patients should be kept in mind.

c. Nurses.—The frequent occurrence of typhoid fever among nurses suggests that the care usually taken

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is not sufficient. To reduce or prevent this infection is difficult. Careful instruction as to the danger, strict regulations as to disinfection, and thorough oversight to ensure that these regulations are carried out, are all important. One difficulty is that the nurses often have too much to do. This is especially apt to be the case with the night nurses. Disinfection after each handling of a typhoid-fever patient means time, and this the nurse on a heavy ward may not seem to be able to spare. Whenever possible the nurses attending to the typhoid patients should do that alone. The wearing of rubber gloves should reduce the danger of infection. They could be used for the greater part of the work done, especially that connected with the changing of clothing, handling of bed pans, urinals, etc. In giving sponge or tub baths their use is not so important.

d. Orderlies.—It has always been a surprise in the Johns Hopkins Hospital that so few of the orderlies contracted typhoid fever. In any hospital they must always be regarded as likely means of carrying infection; being usually overworked, apt to be careless in any case and thoughtless about danger, they require constant watching. Even with stringent regulations, it is hard to be sure that orders are obeyed. There is no doubt that as much as possible of the waiting on typhoid-fever patients should be done by the nurses. Strict oversight and great care in the handling of the ward utensils are most essential points.

e. Ward Utensils.—These should be rigidly isolated. The bed pans, enema nozzles and urinals should be kept for the use of the typhoid-fever patients only. The thorough disinfection of these is most important. Edsall mentions in the article already noted an apparatus devised by Dr. C. P. Noble in which the bed pans can be boiled. The urinals and nozzles should be boiled and kept in an antiseptic solution. The same rules as to isolation and disinfection should apply to the thermometers. These measures are important, not

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only for the protection of other patients, but also for that of the nurses and orderlies.

f. Food.—No one who is handling typhoid-fever patients should be allowed to have anything to do with the food supply for the other patients. In almost all hospitals this is difficult to carry out, but it should be done. If a patient with smallpox was concerned, there would be no doubt of this being carried out, but we are accustomed to typhoid fever. The easy possibility of food infection was well shown by an instance which came under my observation. A patient who had a chronic cystitis due to the typhoid bacillus, anxious to be of some help in the ward, was found to have been giving water, into which he had put pieces of ice, to other patients. Luckily no infection followed.

g. Flies.—Here is a problem difficult of solution. The easiest way is to keep the flies from the typhoid-fever patient. By screens the number in a ward can be kept to a minimum, and by keeping netting over the patient the chances of the flies in the ward getting at him are reduced. Even with screens it is difficult to keep the flies away when necessary things are being done. Care should be taken to prevent flies from lighting on the dejecta before these are sterilized, and the bed pans should be covered, especially as they are sometimes left standing for some time before being sterilized.

h. Disinfection of Stools and Urine.—The methods for this need not be discussed here. The important thing is to see that they are carried out. For this, constant oversight is necessary, especially of the orderlies.

PRIVATE PRACTICE.

Here the problem of prevention of infection may be much easier or almost impossible of solution. In a wealthy home, with two trained nurses, there is not very great difficulty. The rules of the hospital can be carried out rigidly. But in the homes of the poor it is quite another matter. The mother of a large family

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may have to nurse the patient and attend to the rest of the family. Take some of the conditions one finds. The patient is nursed by one of the family, possibly well-meaning but ignorant; flies are numerous, both about the patient and on the food; the urine and feces are perhaps thrown out on the ground in the country or in the ordinary privy, the flies being there also. Who can feel any certainty of being able to prevent infection under such circumstances?

Still, much may be done. The danger of infection should be emphasized every day, and, if possible, those waiting on the patient prevented from preparing the food for the family. Specific written directions as to the rules of isolation and disinfection should be given. These should be put under the headings: (1) for the attendants, (2) for the food utensils, (3) for the clothing, sheets, bed pans, etc., and (4) for the urine and stools. The physician should himself demonstrate how the dejecta are to be handled. It should be possible to prevent them from being thrown out on the ground or into an open privy, whether thoroughly disinfected or not. The possibility of infection of a water supply must always be remembered. To keep flies away it is usually possible to have the room screened. If wire screens can not be obtained, cheese-cloth can be put over part of the window to hinder the entrance of flies. Netting can also be used over the patient.

PRECAUTIONS IN CONVALESCENCE.

It is the duty of every man who treats patients with typhoid fever to take every means in his power to be sure before the patients are discharged that they are not typhoid "carriers." This is easy as regards the urine, but very difficult as regards the stools. To every patient urotropin should be given during the course and in convalescence. By doing this we can be reasonably sure that the urine is free of bacilli, and by giving large doses (75 gr. per diem) we may do much

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to destroy them in the gall bladder. In doing this we should watch constantly to avoid the production of hematuria.

Certainty as to the stools being free of bacilli is difficult to attain. Even in hospitals this may seem impossible. It is a large question and perhaps will have to be a matter of inspection by the state. To hope for this may seem utopian and yet it should come. It would be done in case of plague, but that is an unfamiliar story to us; typhoid fever is an every-day matter and familiarity brings carelessness.

There is no question of the difficulties that meet us when we endeavor to make sure that no other individual stands in any danger of infection from our typhoid-fever patients. It is so easy to rest content with bringing the patient through the attack; that is something which shows and there is no applause for the prevention of cases of typhoid fever which might have been. Yet if the statistics of any community show a decreasing incidence of the disease, every practitioner in it who has done his part to bring this about can have the consciousness that to him belongs some of the credit. Must not this be the highest reward for many of the triumphs of preventive medicine?

807 St. Paul Street.

DISCUSSION.

Dr. Alexander Lambert, New York: Feeding experiments were carried out under my care a year ago on a number of patients. In giving a diet absolutely free of milk, in which sugar was abundant, a remarkable point was the absolute lack of meteorism; the abdomens were excavated instead of swollen, the delirium diminished rapidly, the patients were clear-headed, required no medication and lost weight to a small extent. One boy went two and a half weeks with a loss of about five pounds in weight. Dr. McCrae's stand as to diet is the stand of the famous old woman who said that she was always open to conviction, but she would like to meet any one who could convince her. I think that if Dr. McCrae will leave out the milk he will be convinced that there is a better diet and a most generous one, of rice, broth, sugar, butter and a few crackers; it will open his eyes to the possi-

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bilities of a diminution in the toxicity of typhoid fever, a diminution of the delirium and meteorism in the majority of patients.

Dr. H. B. Weaver, Asheville, N. C.: It is said that there are lies, exaggerated lies, and statistics. I should hate to give my statistics in reference to typhoid, but my experience has given me some positive ideas regarding the treatment of typhoid with what I call a mixed diet. My plan of treatment is to begin the case with a mild laxative, of calomel, not with the German rule of heroic doses of calomel. After the alimentary canal is cleared then I begin with plenty of water on the inside, and when hyperpyrexia arrives with plenty of water on the outside. As to the diet, I give enough milk, if well borne, with plenty of chicken broth with rice cooked in it, and a few crackers now and then. This will suffice for all cases of typhoid fever. In reference to the bowels, I never give a purgative, but rely on salt solution enemas, Nature's remedy. How do we know whether the system has enough chlorid of sodium remaining to sustain the vitality? It is said that all normally healthy persons excrete from three to four drams of chlorid of sodium daily; may it not be possible that we fail to give enough chlorid of sodium to patients during these four weeks of typhoid fever? Therefore, I mix a little salt with chicken soup and broths, which the patients take with avidity. It seems to me that they relish that food and it keeps them along to convalescence. I let drugs alone, as a rule; pay no attention to the coal-tar remedies, but rely on cold water on the outside and plenty of good water on the inside, with a mixed diet. This treatment will get a majority of patients through successfully.

Dr. E. P. Joslin, Boston: There is one point in this excellent paper to which I must take exception, and that is the recommendation for drinking excessive quantities of water and the excretion of immense quantities of urine in the twenty-four hours. Such a procedure puts a great demand on the individual. If we allow our patients eight out of the twenty-four hours for sleep, a little calculation will show that to void six quarts of urine in the remaining sixteen waking hours the bladder would have to be emptied or a glass of liquid drunk every twenty minutes.

Dr. W. S. Thayer, Baltimore: The importance of early and complete cooperation between physician and surgeon is, after all, a point which relates not only to the complications of typhoid fever, and especially to suspected cases of the bowel. but to practice in general. What one might say regarding perforation in typhoid, one might also say as well with regard to appendicitis. It is important to remember that whenever in such cases there is any thought of surgical interference we should call in our friend, the surgeon, at once. The first impulse of most conscientious physicians and surgeons

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is to avoid operation unless it is absolutely necessary, and each new man that sees the case passes through this period. I recall vividly a case in point. When I was a resident in a hospital, about fourteen years ago, at a time when early operation for appendicitis was not so common as it is to-day, I was called early one morning to see a nurse. She had an acute appendicitis. I hesitated, however, to send for the surgeon immediately, thinking that she might be better within a few hours. Two hours later I sent for the surgeon. He thought that early operation would be wise, but did not want to hurry and put it off for a few hours more. But in a few hours our minds were made up and the patient was prepared for the operation, when my chief came in and, in turn, said, "Let's wait a little while," and put it off until the afternoon. In the afternoon all were agreed as to the advisability of immediate operation, when the surgeon-in-chief arrived. The surgeon-in-chief, by a like conservative impulse, said, "Let's wait until to-morrow morning." On the following morning when the patient came to operation there was a general peritonitis, and before it was over she had three grave operations and was at the point of death. She is still living, but her life was nearly sacrificed because four conscientious men, seeing her one after another, all wanted to wait a little while; any one, had he seen the case when I first saw it, would have advised operation within an hour or two. The physician should always summon his surgical colleague the moment he suspects the eventual necessity of an operation. Such a procedure saves many lives.

Dr. Lawrence Litchfield, Pittsburg: I heartily endorse, in the main, Dr. McCrae's paper. As to calcium lactate, I even go so far as to give it hypodermically in severe cases. I have seen three cases in which large doses given hypodermically, with normal salt solution, seemed to bring very good results. I can not pass over his objection to initial purging. What he says is very suggestive, but I have the histories of over a thousand cases in which initial purging has been the rule and in which troublesome diarrheas have occurred very rarely. As to what has been said about not purging at all, I gave 150 consecutive patients daily morning doses of sulphate of magnesium, and the mortality was as low as any I ever had, and the hemorrhages and perforations were below the average. Of course, 150 cases are far too few to base conclusions on, but they are enough to show that a laxative is not a deadly thing in typhoid fever. If Dr. Ewing's position is correct, that the nitrogenous waste in typhoid fever is not from the toxins of the invading bacteria, but from autointoxication, largely from the digestive tract, it seems that a great deal might be said in favor, not only of the initial purge, but even of laxatives during the course of the disease. In speaking of flies, Dr. McCrea mentioned keeping them away from the patient

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and the food, but most important of all is to use covered bed-pans and to keep the stools away from the flies. One point as to the treatment of perforation: On account of difference in the absorptive power in different parts of the peritoneal cavity, as soon as there is a suspicion of perforation the head of the bed should be raised and kept elevated, so that there may be drainage into the pelvic cavity and not the upper part of the peritoneal cavity, which is more vulnerable. I should think it would be dangerous to roll a patient about in the search for movable areas of dulness with the effect of spreading the infection over the entire peritoneal cavity, if a leak should have occurred. As to the large amounts of water, I agree with Dr. Joslin. Of course, typhoid patients should have enough water. You remember Dr. Thayer's suggestive paper some years ago on "The Relation of Typhoid Fever to Arteriosclerosis." I think that we have all seen protracted cases of typhoid in which the radials became palpable under our very fingers. If this is true, would not the overloading of the system with so much water necessitating in extreme cases as practiced in Cleveland, the elimination of four to eight quarts during the twenty-four hours, put an unnecessary and excessive strain on the heart and favor the development of arteriosclerosis?

Dr. Henry B. Favill, Chicago: So far as I know there are only two subjects on which I am unreasonable. One is automobile scorchers and the other lead and opium in hemorrhage. There is no question about the authority, as far as authority goes, on this question of lead and opium, particularly opium, in typhoid hemorrhage. So far as my experience leads me to a judgment, it is a fact that the locking up of the bowel after hemorrhage, with opium, to which the lead is so far as it goes an additional objection, is a pernicious practice not justified by either experience or theory. Three objections exist in my mind: First, it increases the meteorism; second, it tends to obstruct the excretions; third, it frequently locks in the colon a mass of blood which undergoes decomposition to such a degree that it is not to be compared with anything we meet clinically. It is a dreadful condition, hypothetically and, I think, practically, to be superinduced in a serious infective disease.

Dr. John A. Witherspoon, Nashville, Tenn.: I feel much like the boy who wrote the essay on snakes in Ireland and said, "There are no snakes in Ireland." There is no treatment of typhoid fever. I agree with Dr. McCrae when he says, let each case be its individual lesson to us. That is all right, but in his paper he did not, to my mind, carry out the idea with which he started. I heartily agree with Dr. Lambert when he condemns the use of milk, especially sweet milk, in typhoid. I believe that we would have very little meteorism, that we would have very little intestinal disturbance, if we

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properly fed our patients. Sweet milk has been, in my experience, one of the most universal disturbers both of stomach and intestines of any nourishment I have seen used in typhoid fever; therefore, I have long since ceased to use it, because every case I have demands a mode of treatment to get rid of symptoms directly produced, in my judgment, by such treatment. I believe that Dr. McCrae, who gave us an elegant way of relieving the distended stomach with the stomach tube, if he feeds his patients properly, will rarely find any necessity for using the stomach tube. You will seldom find much gas and diarrhea if you will avoid disturbing the nutrition by improper feeding of your patients. Another point on which I could not agree with Dr. McCrae is the use of hexamethylenamin to kill the bacillus in the gall bladder and elsewhere. I do not believe that it would be possible for hexamethylenamin to destroy the bacteria or bacillus typhus in the gall bladder unless you carried the treatment to such an extent that in the preparation of subjects you would practically have to prepare the dead subjects, as we would the cadaver, to kill the *Bacillus typhosus* with it. While I have had a little experience with hexamethylenamin, it has not given me the results it seems to have given Dr. McCrae. I believe in the management of typhoid fever; there can be no objection in the earliest part of the disease to the initial purge; it has been a universal practice, and I believe does aid in the future welfare of the case. Then as few drugs should be given as possible, and proper nutrition, which, in my judgment, should be egg albumins, broths with rice, etc., in buttermilk, and things of that sort will keep down the necessity for too many drugs. The fewer drugs used in this disease the fewer will be the complications. I endorse everything else in the paper, except excessive drinking of water. I do not believe that it is sensible to deluge the stomach of a patient with water or anything else.

Dr. Thomas McCrae, Baltimore: My experience has been that the large amounts of urine passed do not give any distress to the patients. The ordinary typhoid patient is wakened every three hours in the night to take nourishment and can void at that time. I agree with what Dr. Litchfield said about the advantage of the administration of calcium lactate hypodermically in some cases. In regard to the danger of overloading the circulation with water, I have never seen any evidence of it. What is it that leads to the changes in the arteries? Is it not the presence of toxins? The more we can reduce the toxemia, which you will grant hydrotherapy does, the more we reduce the danger to the blood vessels. Clinically I have not seen any evidence of harm to the circulation. Dr. Witherspoon implied that the patients in whom I had seen distention of the stomach were on a milk diet, but, on the contrary, the majority of them were being given predigested

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foods, beef tea and broths. Regarding the point about hexamethylenamin not having any effect on typhoid bacilli, it seems to me that if one point has been established it is that hexamethylenamin does kill out the bacteria in the urine. I think that this has been too definitely proved for us to have any doubt of it. In regard to the use of adrenalin in hemorrhage, I have never been able to persuade myself that it is of value either theoretically or in practical results. As to the amount of hexamethylenamin I do not think we know as yet; I mentioned 75 grains a day and perhaps we might go higher, but we have not had enough material as yet to enable us to pass final judgment. This disease has so many phases and such varied symptoms that it is natural we should have various ideas about treatment. The consoling thing is that so many of the patients recover under so many different treatments. It shows that all the truth does not rest in one method. We are all agreed, however, as to the importance of preventing infection from our patients.

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THE SERUM TREATMENT OF MENINGITIS.

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BALTIMORE.

Flexner's antimeningitis serum has been in use for epidemic cerebrospinal fever now for one year. A final opinion of its value as a therapeutic measure must be reserved until the number of cases in which it has been used is very large. Our experience at the Johns Hopkins Hospital with a small series has been so striking, however, that Dr. Barker has asked me to present it to you.

The Board of Health statistics for Baltimore do not show the present epidemic to be more severe than those of previous years. In fact, we feel that the cases are rather sporadic than epidemic. And yet to date we have had twenty-one cases in the Johns Hopkins Hospital since January 1, compared with thirty-three cases in the previous nineteen years of the hospital. This we might mention as the first effect of the serum. The knowledge of its use has led local physicians to hurry their cases to the hospital and so enabled us to get them early in the disease—a very important factor in the outcome.

Of the thirty-three patients treated simply by lumbar punctures in the previous years of the hospital, twenty-one died and twelve recovered, a mortality of 64 per cent. The mortality for the individual years has varied from 43 per cent. to 100 per cent.

With this may be compared a mortality of 14 per cent. for the twenty-one cases treated with the antimeningitis serum in the past five months. Three of the

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twenty-one patients have died. One of the three was a fulminant case, in the class regarded by Flexner as beyond the reach of treatment. The second had a complicating bronchopneumonia of both lungs on admission and died in forty-eight hours. The third was a boy 29 months old who received his first injection of serum on the fourteenth day of the disease, when he was unconscious, having convulsions, and practically in extremis. He died of a respiratory paralysis in seventy-two hours; even in his case two injections of serum had succeeded in clearing the spinal fluid of organisms and giving sterile cultures.

As to age, twelve of the twenty-one patients were children under 12 years. Of these but one died, a mortality of 8 per cent.

Seventy per cent. of the cases not treated by serum have had complications, mainly bronchopneumonia, whereas eight of the twenty-one serum cases, 38 per cent., suffered from them as follows:

Otitis media	3
Pneumonia	2
Both otitis media and pneumonia	1
Arthritis	1
Acute myocarditis	1

One of the patients with pneumonia had a metastatic infection of the right eye, but the terrible sequelæ of former years — palsies, mental defects, deafness and blindness—were rarities. The only sequelæ in the twenty-one cases were two of deafness and one of blindness.

Much more striking than the percentages of mortality, however, have been the effects observed at the bedside and in the laboratory in each individual case.

It has been our rule to do a lumbar puncture as early as possible in every case with symptoms suggesting meningitis, and to inject serum, giving the patient the benefit of the doubt. By this routine one patient with pneumonia, one with typhoid fever, two with pneumococcal meningitis, one with influenzal meningitis, and

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six with tuberculous meningitis have received serum. In no one of these cases has any bad effect resulted.

The serum has been injected by a syringe connected with the lumbar puncture needle. In most cases as much serum has been injected as spinal fluid removed, not exceeding 30 c.c.; following the suggestion of Dr. Flexner. But in twelve instances, because of the severity of the symptoms and the height of the temperature—in fact, because we thought it was needed—the amount of serum injected has exceeded that of the spinal fluid removed. Strangely, notwithstanding this fact, the so-called pressure signs and symptoms have been relieved by this treatment.

Many of the patients are temporarily upset by the puncture and injection. They complain of pain in the knees, hips and about the rectum during the injection, evidently referred pains from the lumbosacral roots. These sometimes persist several hours. A slight temporary rise in temperature often follows the injection. Urticaria and erythematous eruptions are not uncommon.

It has taken from twelve hours to three days to reap the benefit from the serum. All favorable cases react to a certain extent after one injection. Some cases need but the one injection. Two cases have required six injections and one seven. We believe the serum should be given daily until the drop in temperature and the disappearance of symptoms and signs indicate that the process is arrested. And it should be renewed at any sign of flare-up.

1. The effect on the *temperature* has been to cause a fall in one of two ways—either abruptly or by lysis. Eight cases terminated abruptly and eight by lysis. In the other five the temperature remained elevated—in two due to complicating pneumonia. The other three were fatal. One case remained normal in temperature after a single injection, but the majority show a rise

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the next day and require from two to six injections to preserve a normal temperature.

2. With the fall of temperature, in three to twelve hours after the first injection, the *symptoms and signs* begin to clear. The symptoms — delirium, headache, pain in the neck and back, and the general hyperesthesia — disappear with remarkable rapidity. The signs — strabismus, stiffness of the neck, retracted head, opisthotonos, and the Kernig sign — are more persistent. The Kernig is often the last sign to disappear. The result is the unusual picture of a child, bright, cheerful, and alive to its surroundings, but with a stiff neck and back, occasionally in opisthotonos.

3. The effect of the serum on the *spinal fluid* itself is most interesting. Three changes are brought about:

First, the polymorphonuclear leucocytes are increased in the spinal fluid. This is only after the first injection, and they disappear in the process of healing. From 200 cells to the cubic millimeter they have been increased to as many as 4,000. The influence of this on the leucocytes in the circulating blood is striking. A high leucocytosis, 30,000 to 40,000, is reduced by the demand in the spinal fluid; a low one, 16,000 to 18,000, is increased. In every case there is a very constant, positive chemotaxis for polymorphonuclear leucocytes in the spinal fluid. This has been observed in one case of influenzal meningitis. In six cases of tuberculous meningitis the clear spinal fluid with predominating small mononuclear cells has become clouded with polymorphonuclears after serum, and the small mononuclear cells have totally disappeared. The serum caused no evident change in the two cases of pneumococcal meningitis.

Second, the meningococci, both extracellular and intracellular before serum, become entirely intracellular, so that it is often difficult to find organisms outside of cells in specimens after serum. This was observed also in one case of tuberculous meningitis and in the influenzal meningitis.

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Third, as they become intracellular they are being destroyed. They no longer stain deeply and distinctly, but are ill-defined and hard to see. They resemble granules rather clear-cut diplococci. This is evidenced by the cultures. The number of colonies from approximately the same amount of centrifugalized sediment are reduced from 200 to 300 down to 8 or 10 after one injection of serum. Most cultures have been sterile after two injections, several after one.

CONCLUSIONS.

In conclusion, from this small experience, we may briefly summarize our impressions as follows:

1. All cases of meningitis in which meningococcus infection is suspected should undergo lumbar puncture and serum injection as early as possible.

2. The serum does no harm in cases not of the meningococcal type. It may do good.

3. The course of the disease is changed by the serum. The long drawn-out chronic cases are not seen, and the terrible sequelæ—often worse than death—are rare.

4. As to the character of the serum, the rapidity with which signs and symptoms disappear suggest an antitoxic property; the positive chemotaxis for polymorphonuclear leucocytes, and the promoted phagocytosis are most definite and constant features; finally, the reduction in the number of diplococci, the change in their staining properties, and the loss of viability speak for a bactericidal power—although it is a question if this may not be explained by the phagocytosis.

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SERUM TREATMENT OF EPIDEMIC CEREBRO-SPINAL MENINGITIS.

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Previous to the work of Flexner in this country and that of Kolle and Wassermann and Jochmann on the continent, little had been accomplished in the production of a serum curative for epidemic cerebrospinal meningitis. The experiments of Bonhoff and of Lipierre, while suggestive of results, were too incomplete and unsatisfactory to warrant conclusions that they were working with a serum of protective and curative value. They were unable to reproduce the disease experimentally in animals in a form simulating that disease in human beings, and there is some doubt as to whether their control animals, for the most part guinea-pigs, died from toxemia or from infection.

THE SERUM.

As a result of the epidemic of cerebrospinal meningitis which devastated greater New York during the winter of 1904 and spring of 1905, in which there were about four thousand cases with 3,429 deaths, Dr. Flexner, as a member of a commission appointed by the Heath Department of New York City, undertook an experimental investigation of epidemic meningitis, with the result that he proved conclusively that this type of cerebrospinal meningitis could, by direct inoculation into the spinal canal, be transmitted to monkeys in a form closely resembling that found in human beings. Furthermore, he was able to produce an antidotal serum

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for the meningococcus which, when inoculated in certain quantities at the same time as an otherwise fatal dose of living cultures of the meningococcus, would in almost all cases prevent the disease from terminating fatally in monkeys. He also could save monkeys inoculated with a lethal dose of living cultures of meningococcus when serum was injected into the spinal canal not later than six hours afterward.

Serum used in this series of cases was furnished by Dr. Flexner and was in brief made as follows: Horses were injected first subcutaneously, then intravenously, with gradually increasing doses of living meningococci. Later subcutaneous injections of an autolysate was used in gradually increasing doses. Many different strains of meningococci are employed in preparing the living culture and the autolysate for inoculation. After months have elapsed the horse is bled, the serum collected and bottled ready for use.

SERIES OF CASES TREATED.

The serum was first used systematically by me in a series of cases beginning April 2, 1907, at Castalia, Ohio, where an epidemic of cerebrospinal meningitis had created such havoc that half the population of the village of six hundred inhabitants had fled in terror. Between the months of January and April, 1907, 18 cases of meningitis developed. Of the 18 patients, 12 died and six recovered, a mortality of 66.7 per cent., a recovery of 33.3 per cent. Serum was used in three cases. All the patients recovered. In the 15 cases in which the serum was not used, 12 patients died and 3 recovered, a mortality of 80 per cent., and recovery of twenty per cent.

In the first few cases treated, from 5 to 10 c.c. of serum was injected at a dose, but wider experience showed it to be safe to use large amounts, and then from 15 to 30 c.c. was used at one injection, provided that much fluid was withdrawn. These injections were

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usually repeated at daily intervals until acute symptoms subsided and the spinal fluid became clear. In some instances two injections were made daily. When the meningeal symptoms disappeared and the temperature subsided, the further use of the serum was discontinued until a rise in temperature or increase in meningeal symptoms made it seem advisable to again employ it.

Altogether, the serum has been employed by me in 32 cases. Of the 32 patients one is still in the acute stage of the disease and can not be considered in this report. Of the 31 cases to be considered, in 30 the diagnosis was confirmed by finding the characteristic Gram-negative diplococci in coverslip preparations, and in almost all cases cultures were positive. In one case, clinically typical of cerebrospinal meningitis, with marked petechial eruption, only a few drops of bloody serum was obtained by lumbar puncture, from which nothing definite was made out. The boy's mother however, had nursed a fatal case of this disease two weeks previous to the onset in him.

That these cases were not mild ones, but of marked severity and a severe test of the therapeutic value of the serum is made evident by the fact that when serum was administered 17 of the patients were comatose, 3 unconscious and wildly delirious, and 12 semiconscious or conscious with great irritability.

Many of these cases were seen in the outlying and poor districts, where it was impossible to obtain as complete records in regard to temperature, pulse and respiration as desirable, though as a rule the records are complete enough to enable one to follow the progress of the cases satisfactorily. A good proportion of the cases were under constant observation at the various hospitals in Cleveland.

Eleven of the 31 patients died and 20 recovered—a mortality of 35.5 per cent. and a recovery of 64.5 per cent. Four of the comatose patients were moribund at the time of the administration of the serum, dying

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within a few hours. Three of the cases in which the patients were moribund were of the fulminating type and were seen forty-eight or less hours after onset. A fifth was a chronic case of nearly four months' standing, in which the patient was blind, deaf, comatose and a mere breathing skeleton at the time of administration of the serum. In a sixth case of thirty-nine days' duration before serum was employed, chronic hydrocephalus had already developed. Subtracting these 6 cases, manifestly unfair tests of the treatment and hopeless so far as serum therapy is concerned, there would be 25 cases with 5 deaths, a mortality of 20 per cent. and a recovery of 80 per cent.

Twenty-four cases were treated ninety-six or less hours after onset. Of these patients 16 recovered and 8 died, a mortality of 33.3 per cent. and recovery of 66.7 per cent. The four moribund patients were included in this group. Subtracting them, there would be 20 cases with 4 deaths and 16 recoveries, a mortality of 20 per cent. and recovery of 80 per cent.

Eighteen cases were seen seventy-two hours or less after onset of symptoms. Fourteen of the patients recovered and there were 4 deaths, a mortality of 22.2 per cent. and recovery of 77.7 per cent. Three of the moribund patients fell within this group. Deducting these, there are 15 cases with 1 death, a mortality of 6.6 per cent. and recovery of 93.4 per cent.

Thirteen cases were seen forty-eight hours or less after onset of symptoms. Nine of these patients recovered and 4 died, a mortality of 30.7 per cent. and recovery of 69.3 per cent. Three of the moribund patients were included in this group. Subtracting these, we have 10 cases with 1 death, a mortality of 10 per cent. and recovery of 90 per cent.

Five cases were seen twenty-eight hours or less after onset of symptoms. All of these recovered, a recovery percentage of 100 per cent.

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Eleven of the 31 cases developed in children under 5 years of age. Six of these recovered and 5 terminated fatally, a mortality of 45.5 per cent. and recovery of 54.5 per cent. In these 5 cases which terminated fatally 4 patients died of chronic hydrocephalus, late in the course of the disease, and a fifth case died during the acute stage of the disease.

The average duration of the disease in cases of recovery seen twenty-eight hours or less after the onset of symptoms, when treated with the serum, was twelve days; above twenty-eight hours and including forty-eight hours, nineteen days; above forty-eight hours and including seventy-two hours, forty-nine days. As most of the cases seen later than seventy-two hours died, a satisfactory statistical chart of cases recovering can not be compiled at this time.

Fever terminated by crisis in 11 cases and by lysis in 9 cases. In one case the temperature was normal at the time of administration of serum and afterward.

Of the 11 fatal cases 4 patients died from chronic hydrocephalus, and 4 were moribund at the time of administration of the serum. One patient in the acute stage of the disease died shortly after the administration of the serum, and in this case there is a possibility that the severe chill, cyanosis and rise in temperature to 106 degrees was produced by the bactericidal action of the serum on the numerous meningococci present and liberation of more endotoxins than could properly be taken care of by the patient. In one case death occurred in the chronic stage of the disease nearly six months after onset. Acute dilatation of the heart and pulmonary edema produced death during the acute stage of the disease in the last case.

In this series of cases the youngest individual was 3 months old and the oldest 28 years of age.

The onset was with marked gastrointestinal symptoms in six cases, marked diarrhea and vomiting being present.

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Petechial eruption alone was present in 11 cases and associated with hemorrhages into the skin in 3 additional cases. A petechial eruption associated with herpes labialis was present in one case. A petechial, hemorrhagic and herpetiform eruption were all present in one case. A petechial eruption associated with erythematous eruption was present in one case. An erythematous eruption only was present in two cases. A macular eruption was present in one case. Mottling of the skin and herpes labialis were associated in one case. In two cases mottling alone was present. Nine cases were unassociated with skin eruptions. Surprisingly few patients had herpes.

In two cases well-marked urticarial eruption developed as a result of the administration of the serum. In one of these cases the eruption came on fifteen days after the injection of the serum, and in this case practically all the serum administered was given subcutaneously. In the second case the urticarial eruption developed one week after 35 c.c. of serum had been administered intraspinally, the child being perfectly well in other respects at this time.

Sequelæ were present in three cases. In Case 1 a left-sided foot drop developed, which is gradually improving. In Case 15 slight impairment in hearing persists. In Case 31 a marked suppurative arthritis of the left knee is rapidly clearing up under treatment by aspiration and injection of serum directly into the joint.

Examination of the spinal fluid in all cases showed the polymorphonuclear neutrophilic leucocyte to be the predominant cell with varying numbers of endothelial cells present. The largest number of endothelial cells found were in the fluid obtained from Case 31, in which diplococci were very few and hard to find. In many cases these endothelial cells were phagocytic for meningococci and not infrequently contained polymorphonuclear leucocytes in various stages of disintegra-

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tion. In a very few cases with a diminution of turbidity of the spinal fluid an increase in lymphocytes was noted and in one case, well along in the course of the disease, differential count showed 98 per cent. of lymphocytes. As a rule the neutrophilic leucocytes are very much in excess, and as the fluid becomes clearer, while they diminish in numbers, differential count still shows them to be approximately 90. per cent. or more of all cells. The number of diplococci present in the spinal fluid seems to have no bearing on the severity of the clinical symptoms. In some cases in which there was most marked petechial eruption, coma and meningeal symptoms, it was difficult to find organisms. Occasionally organisms could be found only after cultures had been made or after incubation for twelve hours of the original spinal fluid. On examination of such incubated spinal fluid one often finds very numerous intracellular and extracellular meningococci, which can then be cultivated more readily.

In most cases in which recovery takes place after the injection of serum the spinal fluid progressively becomes clearer and diminished in amount. In several cases, especially those in which few or a moderate number of meningococci were found, these could not be cultivated subsequent to the injection of serum, though they grew readily at first. In such cases, as a rule, the diplococci do not stain well. At other times growths could be obtained until after the second or third dose of serum had been administered, and occasionally when considerable amounts had been given after longer intervals of time had elapsed. In cases in which the microorganisms, both intracellular and extracellular, are present in exceedingly large numbers, it has been my experience that the prognosis is not so good, even though the patient may present no worse symptoms clinically than other patients from whom fewer organisms have been obtained. In such cases rises in temperature following the administration of serum have

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taken place several times, and in one case in particular I could not help but feel that more endotoxins had been liberated than could be properly taken care of by the antitoxic properties of the serum or by the patient himself. In such cases I should feel like giving a small amount of serum intraspinally with frequent repetitions and larger amounts subcutaneously. Or, if large amounts be used intraspinally they should be sufficiently large (for example, 30 c.c. or more) to provide antitoxic properties enough to neutralize the endotoxins liberated. It should be advisable, also, to administer considerable serum subcutaneously.

Absence of fever does not mean necessarily a betterment in condition, as frequently a very purulent spinal fluid is withdrawn in cases with normal temperature when seen.

In several instances in which it has been difficult to find meningococci on first puncture and in which cells containing the meningococci contained very few, after the administration of serum and subsequent withdrawal of fluid, I have repeatedly found cells packed with meningococci, though possibly there were no more phagocytic cells than on first examination. This would indicate that opsonins played a definite part in the process of immunization. The poor staining of the meningococci seen after the use of the serum would seem to point to definite bactericidal properties in the serum.

Some of the cases presented features of unusual interest, and I shall briefly mention them.

In Case 2, which was almost in the third week of the disease, the disease terminated abruptly after the withdrawal of fluid and injection of serum.

Case 8 was interesting because a young man desperately ill was cured by subcutaneous injections of serum, only 5 c c. having been given intraspinally. The subcutaneous method was used because frequent attempts to withdraw fluid by puncture were unsuccessful, only a few drops of bloody serum being obtained.

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In Case 12 the question arises whether the liberation of endotoxins following the injection of serum had anything to do with the appearance of a marked chill, cyanosis and rise of temperature to 106 degrees with death shortly afterward.

In Case 13 puncture and injection of serum was made in less than two hours after development of meningeal symptoms with a result that the disease was promptly arrested in its progress in spite of the fact that there was much pus present and fairly numerous meningococci.

Case 17 is of interest because sharply staining Gram-negative intracellular diplococci were found in the spinal fluid at the time of puncture, approximately four months after onset. Cultivation of these were unsuccessful.

Patient 19, a child seven months old, was discharged apparently well sixty-one days after the onset of the disease, but was readmitted seventeen days after the discharge on account of convulsions associated with twitching of the right side of the face and of the extremities on the right side. There had been four such attacks, beginning six days after discharge from the hospital, and the child was admitted the second time during the fourth attack, which lasted five hours. This attack was promptly checked by lumbar puncture and the withdrawal of 35 c.c. of perfectly clear fluid. No further attacks have since developed.

In Case 23 it was difficult to tell what marked the onset of the cerebrospinal meningitis; whether an acute process due to the meningococcus was engrafted on a more chronic obscure trouble, or whether from the first the condition was due to a meningococcus infection of unusual onset.

In Case 25 a condition of hydrocephalus in which large amounts of clear fluid were obtained by puncture, following the subsidence of the acute meningeal symptoms and which gave every evidence of becoming chronic,

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eventually subsided completely and the child remains well at the present.

The feature of particular interest in Case 29 was the direction followed by the aspirating needle in getting into the spinal canal. Attempts to get the needle in by the direct method in the mid-line, or by the up-an-in method, starting slightly below the mid-line, resulted negatively, and fluid was obtained only when the needle was directed down and out, the needle being inserted below the mid-line between the third and fourth lumbar vertebræ. The child in this case was the subject of congenital lues, and no marked degree of scoliosis was present.

Case 31 is the most interesting and important of the series.

Patient.—M. N., male, aged 28, was perfectly well on the early morning of May 16, 1908.

Onset of Disease.—At 9 o'clock in the morning, May 16, the patient felt sick and was seized with a violent chill. Temperature of 103 F., with a pulse of 100, and normal respirations developed about 3 o'clock in the afternoon of the same day. Patient was seen by Dr. Cheetham at 10 o'clock in the morning. No meningeal symptoms were present at this time. On the evening of the 16th headache developed and at 3 o'clock in the morning of May 17 the patient became wildly delirious and unconscious. At 5 o'clock opisthotonus, Kernig's sign, petechial eruption, with true hemorrhages into the skin, and general rigidity were present.

Clinical Course and Treatment.—May 17: The patient was brought to Lakeside Hospital at 2 p. m. At this time temperature was normal and the pulse 100. The patient was still wildly delirious and unconscious and required the efforts of three men to control him while chloroform was administered and lumbar puncture performed. Forty c.c. of quite turbid fluid was obtained and 30 c.c. of serum injected. Examination of this fluid showed a very rare and rather poorly staining intracellular diplococcus. Cultures were made and the original fluid incubated with the result that typical meningococci grew out in large numbers in the incubated fluid and a few colonies developed on artificial cultures.

May 18: The patient was better. Temperature was normal and pulse still about 100. There was still marked rigidity and

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Kernig's sign was present. Semiconsciousness was present, though at times patient could be aroused and made to answer questions intelligently. At 10 o'clock a second puncture was done and 25 c.c. of still turbid fluid was obtained. Fifteen c.c. of serum was given. Bacteriologic examination of this fluid gave results similar to those obtained at the time of first puncture, except that cultures failed to develop and even in the incubated fluid the meningococci did not increase in numbers. From this time on no further growth was obtained from the spinal fluid.

May 19: A third puncture was made and 45 c.c. of slightly blood tinged, but less purulent fluid was obtained. This came out under considerable pressure. Fifteen c.c. more of serum was injected intraspinally. The patient's mental condition was much brighter. Kernig's sign was still present but opisthotonus and muscular rigidity was less marked and the petechial eruption was beginning to fade. On this day the temperature went up to 100 with a pulse of 100, though the pulse was of a better character than at any time previous.

May 20: The temperature rose to 101, though the patient's condition was gradually improving as regards mental and meningeal symptoms. Lumbar puncture was performed and 25 c.c. of very slightly blood-tinged and still less purulent fluid obtained. Fifteen c.c. of serum was injected.

May 21: The patient's condition was so good that no lumbar puncture was made. Temperature was 101 F., pulse 90.

May 22: The patient's temperature continued to be 101, though all other symptoms were disappearing. Lumbar puncture was performed and 10 c.c. of quite clear fluid was obtained. Fifteen c.c. of serum was administered. The patient's mental condition was perfectly clear and except for very slight rigidity of the cervical muscles, and a still-present Kernig's sign, the meningeal symptoms had disappeared. Temperature still remained about 101 and continued at that point until May 25.

May 25: The temperature reached 103. The patient first complained of pain in the left knee joint. Examination of the joint demonstrated increased surface temperature, marked tenderness on palpation, and moderate bulging of the bursæ around the joint. Ice-bags were applied and the leg placed in a pillow splint.

May 26: The joint was more painful and hot and there was marked fluctuation present. The slightest motion caused excruciating pain. Aspiration was resorted to and 30 c.c. of thick purulent fluid obtained. Microscopic examination of this showed a very rare poorly staining intracellular diplococcus. No other micro-organisms were present. Cultures

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failed to develop even after incubation of the fluid. Fifteen c.c. of serum was injected into the joint through the aspirating needle.

May 27: The patient felt better, though there was still marked fluctuation present and great tenderness on motion. Temperature was 100. Aspiration was again resorted to with a result that about 40 c.c. of still very markedly purulent fluid was obtained. Fifteen c.c. more of serum was injected. Examination of the fluid removed resulted negatively insofar as cultures were concerned. When aspirating on this day lateral pressure was used in order that as much fluid as possible might be obtained. This was not done at the time of the first aspiration. The patient was told that if on the following morning he did not show more marked improvement surgical procedures would have to be resorted to.

May 28: The patient felt much better and there was less fluctuation, tenderness and surface temperature. Aspiration was again resorted to and 10 c.c. of distinctly less turbid fluid obtained, even though lateral pressure was exerted.

May 29: The temperature was perfectly normal and has remained normal since. There was no tenderness on palpation, surface temperature was normal, and patient could move the knee slightly. Aspiration resulted in the withdrawal of 2.5 c.c. of very slightly turbid fluid. Fifteen c.c. more of serum was injected. Since this date patient has had no more tenderness on motion and pressure can be exerted on the knee joint without pain. Bulging has disappeared.

May 31: There was an angle of flexion amounting to 90 degrees and there is every evidence that the joint will be cured with little or no limitation of motion.

Here, then we have an illustration of the specific action of antiserum as applied to one of the most common complications of cerebrospinal meningitis, namely, arthritis, and that, too, of a suppurative character, with a result that so far is truly astonishing. Knowing the feeble powers of resistance on the part of the tissues of the knee joint in warding off infection, I confess that when I saw thick pus withdrawn by my syringe I felt that nothing but surgical intervention would save the joint, for I have little faith in the medical treatment of purulent joints. Having seen so often the beneficial results arising from the administration of this serum when injected intraspinally I saw no reason for not

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trying serum in this locality. While it is too soon to state definitely that there will be no limitation of motion, I feel confident, by reason of the rapid strides made so far, that there will be little, if any. So far as my personal knowledge extends—for I have not as yet had the opportunity of looking up the literature on the subject—this is the first case in which a suppurative knee has been treated by direct injection into the joint with a specific serum of undoubted bactericidal and antitoxic properties. This case, of coourse, opens up the problem of treating suppurative conditions of joints due to other micro-organisms with specific antidotal serum, provided, of course, that such sera can be produced for the given micro-organisms.

In conclusion, I can do no more than say that, so far as I myself am concerned, I have no doubt as regards the wonderful efficacy of Dr. Flexner's serum in the treatment of epidemic cerebrospinal meningitis, provided it is used on patients not moribund or on those in whom chronic hydrocephalus has not already developed. I confidently believe that statistical reports excluding these cases will show that our percentage of recovery will contrast favorably with our previously high percentage of deaths.

Laboratory of Clinical Microscopy, Western Reserve University, Lakeside Hospital.

DISCUSSION

ON PAPERS OF DRS. LADD AND SLADEN.

Dr. William S. Chase, Akron, Ohio: During the epidemic of cerebrospinal meningitis that occurred in Akron in the latter part of April and in the months of May and June, 1907, there were 22 cases of this disease. Of that number, 12 patients received the antiserum intraspinally; 10 did not receive it. Of the 12 treated with the serum, 9 recovered and 3 died, a mortality of 25 per cent. Of those not receiving the serum, 1 recovered and 9 died, a mortality of 90 per cent. Of the 3 patients who received the serum, 1 was moribund at the time of receiving the injection; another case was of the fulminating type, the type that Dr. Flexner has considered hopeless; the third patient received 15 c.c. of the serum twen-

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ty-four hours after the onset of symptoms, and the reaction was as marked and striking as in any case that went on to complete recovery. But this patient died suddenly and without warning. An autopsy was not permitted. If one or two of these fatal cases could be eliminated, there would be shown about the same percentage of recoveries when the serum was used as the percentage of deaths when it was not used. These figures, taken from the same epidemic, he regarded as most impressive. All the patients that received the serum were treated at the Akron City Hospital. The clinical diagnosis in each instance was made by an examination of the cerebrospinal fluid and the detection of the *Diplococcus intracellularis*. In the first case, which immediately followed those seen at Castelia by Dr. Ladd, we, the members of the staff, were in doubt regarding the dosage and did not give over 10 c.c. There was nothing at that time to govern the dosage in human beings. The first 2 cases, while each patient recovered, ran a prolonged course. We were careful at first not to inject any more serum intraspinally than the amount of fluid they withdrew; therefore, in one case 5 c.c. were given as an initial dose. Afterward we disregarded this rule as an unnecessary precaution. Only 2 cases showed any pressure symptoms, and in both of these we were careful not to inject more serum than fluid withdrawn. The effect of the serum when injected intraspinally has already been described in detail by Dr. Barker. I wish to lay special emphasis, however, on the point that the effect of the serum in ameliorating the symptoms can not be given in a statistical report or be depicted graphically on a clinical chart. One must see these cases in order to realize the general improvement coming within twenty-four hours after the injection. In the first one or two cases we wanted to see if the same results followed lumbar puncture without the injection of serum. The reaction was not marked. There was no striking drop in the temperature and no amelioration of mental symptoms. We did this because we had practically nothing to guide us in reaching a conclusion as to the relative merits of the serum. I agree with what the other speakers have said in regard to the necessity of making intraspinal injections early in order to get the best results. But in my series of 12 cases benefit followed the intraspinal injections of the serum even in cases which had run a course of ten or fifteen days. In one case, which had been a very severe one (all the patients treated by the serum were comatose or delirious at the time of receiving the first injection), the patient did not get the serum until the tenth day and then received but one injection. Marked improvement followed and the temperature dropped to normal in twenty-four hours. In another case the injection was made on the tenth day with a similar result. The temperature fell to normal and the patient passed from a period of wild de-

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lirium to one of perfect quiet. He made a complete and quick recovery. What impressed me very much about the cases in which the serum injections were given was the absence of sequelæ. In no case were there any of the eye or ear symptoms which usually follow the epidemics of cerebrospinal meningitis. The only sequela which persisted in any case was in one patient, a partial paralysis of the leg muscles. This case ran a course of five or six weeks. In 5 the cases terminated by crisis; in 4 by lysis. None of the patients received any medication whatsoever, except where it was necessary to give an injection of morphin or hyoscin to quiet the severe delirium.

Dr. Frank S. Johnson, Chicago: I have a patient at present under my care who was treated with the serum. This case had a gradual onset, and it was not until the patient had been in the hospital for some time did we procure the serum. During the early stages the patient, a boy, had no mental impairment whatever. There was a gradual onset of the cerebral symptoms. When he received his first injection, however, he was delirious. Fifteen or 20 c.c. of cerebrospinal fluid were withdrawn and the same amount of serum was injected. After the first injection the patient's temperature fell, but the delirium continued and it was necessary to give a second injection, and more injections; in two weeks this patient had received 200 c.c. of Flexner's serum. Finally the delirium disappeared. After the last injection there was a slightly elevated but fluctuating temperature. This I attribute to an incomplete destruction of the infection or perhaps to the effect of the serum which was given. There was no complication following the trouble, except a slight impairment in the strength of the left arm and left foot. The patient otherwise made a good recovery.

Dr. Edward F. Wells, Chicago: The only case of cerebrospinal meningitis in which I have seen the serum used was at the Cook County Hospital. This patient was severely ill with the ordinary symptoms that attend this malady. There was mild delirium, unconsciousness, high temperature, etc. He had been sick for four or five days when the first injection of the serum was administered. The fluid recovered from the spinal puncture previous to the injection was exceedingly turbid and the cellular elements so numerous that an accurate count was not practical. Following the first injection there was a marked amelioration of all the symptoms and the character of the spinal fluid changed, becoming clear in a remarkably short time. Altogether three injections were given, the symptoms promptly subsiding, and the patient made a prompt recovery. Two other cases were treated at the Cook County Hospital, both with the serum, and recovery followed in these instances as well. Without knowing all the facts in these two cases, I know that both received the serum late, and the

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symptoms were not so characteristic and the serum did not produce the same changes as in my own case.

In estimating the value of any treatment of cerebrospinal meningitis, it is only fair to say that the malady itself would vary greatly in seriousness and dangers from various causes. I have had occasion to observe two epidemics of cerebrospinal meningitis occurring on virgin soil. In both of these epidemics the cases were exceedingly severe and had a high mortality. In both, as time went on, the malady became less severe and there was a larger proportion of recoveries. In Chicago we have had cerebrospinal meningitis with us since the World's Fair, and the disease has been rather mild. At this stage in the estimation of the value of Flexner's serum I am of the opinion that personal impressions should be considered rather than the statistics. I wish mildly to criticize Dr. Ladd in this. When one cuts out of his statistics a certain class of cases, as Dr. Ladd did, much force is lost. I suggest that when one begins to eliminate certain classes in a series of cases, a beginning should be made at the other end by a plain statement that in this series, for instance, 36 per cent. would recover in any case with ordinary or no treatment. Dr. Chase, in his published paper, stated that out of 12 patients 9 recovered under the serum treatment; while of 10 patients who had not received the serum treatment 9 died. Now when such statistics, accompanied by the statement that the physician's opinion, based on personal observation of the cases, was favorable to the usefulness of this serum, was presented to us we should sit up and take notice.

Dr. Joseph Eichberg, Cincinnati: During the last two months epidemic cerebrospinal meningitis has been prevalent in Cincinnati, and from 15 to 18 hospital cases have been treated with the serum. Cultures were taken at the time the first injections were given, and the cases were known to be distinctly epidemic cerebrospinal meningitis, the symptoms usually being very severe when the puncture was made. The observations made on these cases are as yet incomplete, but they substantiate what has been stated in regard to the immediate benefit afforded by the use of the serum. I think it is justifiable, even if later studies do not establish the curative value, to give the serum as soon as the diagnosis is made. The results from the serum in patients over 30 years of age in our series of cases were not as good as were secured in the younger subjects so far as the primary effects were concerned. The best results were obtained in those patients whose ages ranged from 8 to 25 years. In two cases there appeared a papular eruption very much like that of measles, except that the papules were much larger. They were crescentic in shape and tended to become confluent; this eruption appeared in two patients and within twenty-four hours after the use of the serum in both instances. It caused little inconvenience.

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At the point of the introduction of the injection, local anesthesia was at first produced by means of ethyl-chlorid spray; this sometimes results in a deep and extensive ulceration about the point of introduction of the needle, as the local nutrition was interfered with in consequence of pressure after the freezing. After this experience we gave the patient a few whiffs of chloroform and discarded local anesthesia. I think that it is still too early to judge of the curative effects of the serum because of the great variability of the virulence of the epidemics. In the present epidemic the percentage of recoveries is high. But it seems to me that we are justified in using the serum because of the immediate primary change in the symptoms and the favorable turn produced evidently by the serum. There is the immediate relief of the headache, a decline in the fever, a marvelous clearing up of mental symptoms, a subsidence of the delirium, all caused by this serum, reminding one of the clearing up of the symptoms in diphtheria under the influence of the antitoxin.

Dr. D. E. English, Millburn, N. J.: Does Dr. Ladd give 30 c.c. of serum intraspinally at the first injection? Does he give the amount of serum that corresponds to the amount of cerebrospinal fluid removed? Or does he try to take away more fluid than he wishes to give of the serum? Is the subcutaneous dose larger than the intraspinal dose?

Dr. O. M. Gilbert, Boulder, Colo.: I chanced to see a case of cerebrospinal meningitis in a specially severe epidemic in which the streptococcus was more in evidence than the *Diplococcus intracellularis*. The bacteriologist who made the examination first reported back that it was a case of pure streptococcus; but later the diplococcus was found. The giving of 20 c.c. streptolytic serum resulted in recovery. We had no Flexner serum. Eighty per cent. of our patients had been dying. Would not the streptolytic serum be of value when both germs are demonstrated?

Dr. L. W. Ladd, Cleveland: I have had little experience in the use of the Flexner serum in other than the meningococcus type of cerebrospinal meningitis. I have used it in several cases of tuberculous meningitis, but without any result whatever. In one case of meningitis in which streptococci and an unidentified streptothrix were associated I used the serum. The patient was moribund when seen and died three hours afterward. In Wheeling, W. Va., I have seen a case which I thought one of tuberculous meningitis. Lumbar puncture was performed and an increased amount of spinal fluid obtained, under considerable pressure, but examination of the fluid showed a normal cell picture and no micro-organisms could be found on coverslip or by culture. Following the puncture and giving of serum this patient recovered, but was not included in the reported series. I have used the antistreptococcus

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serum in one case only. This was the case of a child who had had otitis media followed by a mastoid infection and later complicated by meningitis. Lumbar puncture was performed and a very thick purulent fluid was obtained in which streptococci were present in large numbers. The antistreptococcic serum was used repeatedly and was followed by some apparent benefit, but death ensued in spite of the serum. The cases which I reported were all meningococcus infections. There were no mixed infections and with one exception the meningococcus was present in all. In answer to Dr. English's question I generally give the serum intraspinally, but sometimes both intraspinally and subcutaneously. When little fluid is removed by lumbar puncture I give more subcutaneously. The amount given intraspinally depends somewhat on the amount of fluid withdrawn. If a large amount is obtained, 30 c.c. are injected intraspinally. I follow the rule of withdrawing the fluid until it flows, drop by drop, as under normal conditions. Serious symptoms have followed the withdrawal of too much fluid at one time. In answer to Dr. Wells' criticism of my paper, I have purposely given statistics, in the first place including all cases irrespective of their condition when first seen and irrespective of the length of time which had elapsed after onset of the case, and then ruling out such cases as were manifestly unfair tests of the efficiency of the serum. Surgeons have had great trouble in educating the medical profession to turn over to them their cases of appendicitis for operation, before symptoms of general peritonitis developed, in order that the result might be most favorable to the patient. The same necessity of early diagnosis and early use of serum is present in the treatment of this disease, and comparative statistics show this strikingly. Ruling out the moribund patients in those seen seventy-two hours or less after onset, 93 per cent. recovered. All of the patients, 5 in number, seen twenty-eight or less hours after onset recovered. Sometimes, of course, it is impossible to make a diagnosis as soon as desirable. With regard to the nature of the substances active in the serum, I do not think that Dr. Flexner has absolutely committed himself. It certainly is true that phagocytosis is stimulated, and in view of the fact that the meningococci after the use of the serum were reduced in numbers and stained poorly and that the patients treated cleared markedly in mentality, it seems reasonable to suppose that the serum is both bactericidal and antitoxic in its action.

Dr. Frank J. Sladen, Baltimore: At a recent symposium on this subject before the American Pediatric Society Dr. Flexner reported an analysis of 380 cases in which the serum had been used. The mortality for 247, the number in this country, is about 27 per cent. At this time also Dr. Dunn of Boston reported 40 cases with 9 deaths, 22.5 per cent. mortality. Dr. Churchill of Chicago had a mortality of 22 per cent.

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for 9 cases. And Dr. Wilkinson of Washington, D. C., reported 3 deaths in 10 cases. The comparison of these statistics with those of the New York epidemic is striking. The mortality for 2,305 cases treated without serum was between 80 and 90 per cent. Dr. Flexner has committed himself, stating that he believes the power of the serum is chiefly bactericidal. He is a pathologist, and his opinion is based mainly on laboratory experiments. Clinically, however, the rapidity with which the symptoms and signs clear up impress us with the importance of the antitoxic property.

Dr. C. F. Hoover, Cleveland: One point brought out in this discussion should be appreciated by every physician, viz., the need of giving the serum as early as possible to anticipate the encephalomyelitis which results from meningo-arteritis which has lasted several days.

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THE DIAGNOSTIC VALUE OF THE CUTANEOUS AND CONJUNCTIVAL TUBERCULIN REACTIONS.

WILLIAM ENGELBACH, M.D.
AND
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In endeavoring to arrive at definite conclusions as to the diagnostic value of the recent local tuberculin reactions, we have made a study of the literature on this subject to May 1, 1908, to which we have added the results of personal observations on 1,242 cases. The review of the literature includes the opinions of nine authors on their results with animal experiments; the reports of 41 authors on 5,032 cases of all ages subjected to these reactions, 3,477 to the conjunctival reaction and 1,546 to the cutaneous reaction. Our own investigations were made on adults only at the St. Louis City Hospital and the St. Louis University Medical School. They consist of 499 cutaneous reaction and 743 conjunctival reactions on 125 positive tuberculous cases, 190 suspect tuberculous cases, 700 other diseases not tuberculous clinically and 90 clinically normal individuals. The sum total of all cases considered is 6,305.

TECHNIC.

Cutaneous Reaction.—The technic according to von Pirquet[1] is so well known that it needs no description. In our own work, after considerable experience, we simplified this technic as follows: The skin is cleaned

1. Berl. klin. Wchnschr., May 20, June 3, 1907.

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with ether, the blood-lancet vaccinator recommended by Pirquet is sterilized in an alcohol flame and the clean skin is scarified until the epidermis is removed, if possible, without drawing any blood. The vaccinator is then wiped dry with ether and again sterilized in the flame; then it is dipped in the 25 per cent. tuberculin (O. T.) and lightly applied to the skin, thereby carrying a small drop of the solution to the skin at a proximal point to the control spot, through which the patient is again vaccinated. We used solutions of 0.5 per cent. phenol, 0.8 per cent. sodium chloride solution, concentrated glycerin bouillon, on which tubercle bacilli had not been grown, and distilled water for control inoculations. Vaccinations with these solutions, as well as the dry method described above, were constantly negative. Our standard of a positive reaction was that of von Pirquet's,[1] i.e., an elevated papule extending more than 5 mm. from the margin of the inoculation.

Other methods which are practically modifications of von Pirquet's have been attempted since his communication. Naegeli and Akerblom[2] demonstrated that by rubbing a dead culture of bacilli on the skin of tuberculous patients they could produce a typical tuberculin reaction. They say that this is a tuberculous reaction, and that the tuberculin is produced by the action of the soluble products of the skin on the tubercle bacilli, and is not dependent on living bacilli in the skin. Moro's[3] method, which he calls the "percutaneous reaction, is made by rubbing a 10 per cent. ointment of old tuberculin (Koch) in lanolin into the skin. A positive reaction is described as "multiple small nodules at the site of inunction" in from 24 to 48 hours. He obtained many more positive results with this than with the conjunctival reaction, and observed no unfavorable effects from it. In scrofula, Oppenheim,[4] Pfaundler,[5]

2. Wien. Therap. Monatschr., January, 1908, xxii.
3. München. med. Wchnschr., 1908, No. 5.
4. Wien. klin. Wchnschr., 1908, No. 32.
5. München. med. Wchnschr., Jan. 26, 1907.

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Moro[6] and Doganoff[7] demonstrated there is a specific hypersensibility of the skin to tuberculin, therefore, a weaker solution should be used.

Conjunctival Reaction.—The most satisfactory technic recommended for adults is the instillation of a 1 per cent. of old tuberculin in boric acid physiologic saline solution, with a repetition of a 2 per cent. solution in the other eye in case the first instillation is negative. Baldwin[8] claims, however, that a 2 per cent. solution is too strong, as he obtained a positive reaction with it in a normal individual who had not reacted to a subcutaneous injection of 10 mg. of tuberculin (O. T.). Cohn[9] and others, on the contrary, used as high as a 4 per cent. solution. He recommends that a 2 per cent. solution should be instilled in one eye, and if the reaction is negative a 4 per cent. solution should be instilled in the other. If the first instillation (2 per cent.) is positive, he controls this by using a 1 per cent. in the other eye.

Calmette[10] first recommended instilling a 1 mg. of a suspension of the dried precipitated toxin. This he obtained by precipitating Koch's old tuberculin with alcohol, drying the same and suspending in sterile water so that one minim equals 1 mg. Schmidt[11] found that a 1 per cent. of dried tuberculin (Hoescht) was equal to a 10 per cent. of Koch's old tuberculin, and ten times stronger than the preparation marketed by the Pasteur Institute at Lille, and produced positive reaction in non-tuberculous cases. Rosenau and Anderson[12] demonstrated that a second instillation in the same eye always gave a positive reaction, even in non-tuberculous cases. The first instillation hypersensitized the eye so that

6. Wien. klin. Wchnschr., 1907, No. 31.
7. Wien. klin. Wchnschr., 1907, xxxi.
8. The Journal A. M. A., Dec. 14, 1907, xlix.
9. Berl. klin. Wchnschr., 1907, No. 47.
10. Presse méd., July 13, 1907.
11. München. klin. Wchnschr., Jan. 14, 1908.
12. The Journal A. M. A., March 21, 1908, l, 961.

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when it was re-instilled it reacted positively on account of the first instillation and not because of a tuberculous process.

The question has arisen in our minds whether those reactions occurring with the second instillation in the opposite eye may not also be due to a general anaphylaxis caused by the first instillation, and not to antibodies which are supposed to be created by the first instillation. Schorer and Noyes in a verbal communication to us said they had obtained positive conjunctival reactions from instilling dried precipitate of a concentrated glycerin bouillon which had not been inoculated with tubercle bacilli. They obtained a precipitate from this by adding alcohol, which produced practically the same results as had a precipitate of the old tuberculin.

In our own work we controlled our conjunctival reactions with a boric acid saline solution and a concentrated glycerin bouillon prepared in the same way as old tuberculin without having tubercle bacilli grown in it. All these control instillations give negative reactions in the four different variety of cases reported. We used preparations from Parke, Davis & Co., Mulford & Co., Pasteur Institute of Lille, and the Alexander Laboratory Co., with practically the same results. Our dilution of old tuberculin was a 1 and 2 per cent. dilution in physiologic saline solution. We made only one instillation in the eye. Our positive reactions would no doubt have been much higher had we inoculated the opposite eye in those cases in which we got negative reactions.

HISTOLOGY.

Cutaneous Reaction.—Burnet's[13] histologic findings or positive reaction in tuberculous guinea-pigs were "necrosis and separation of the epidermis, resembling that which takes place in a burn; beneath this scar was an infiltration of polynuclear leucocytes, characterized by an absence of strong chemotaxis of these cells."

13. Soc. de Biol., 1907, lxii, No. 22.

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Conjunctival Reaction.—Sabrazes and Dupres[14] found the exudate to be of a white, hyaline aspect, consisting of concrete mucous and not fibrin, containing (1) enormous neutrophilic polynuclear leucocytes well preserved, some vacuolated or in fatty degeneration; a great number giving a more or less marked iodophilic reaction; (2) changed or altered epithelial cells; (3) rare or unusual lymphocytic elements and large mononuclear cells with or without vacuoles. Isolated eosinophiles exceptionally. No mast cells. Notwithstanding the polynuclear cytosis and the intensity of the exudate, a prolonged search showed only an occasional rod of a pseudodiphtheretic type which probably has no relation to the toxin. From the above they conclude that it is a toxic conjunctivitis.

ANIMAL EXPERIMENTS.

Lignieres[15] and Valle[16] produced positive conjunctival and cutaneous reactions in tuberculous cattle and horses, and constantly obtained negative reactions in these normal animals. Klemperer[17] observed only one negative cutaneous and conjunctival reaction in a series of tuberculous cattle. Positive reactions have been demonstrated by Valle[16] in tuberculous dogs and rabbits, and by Klemperer in guinea-pigs and dogs. Wildbolz's[18] autopsy findings in rabbits confirmed the value of these reactions. He obtained negative results with both these reactions in twenty normal rabbits which, with one exception, gave positive reactions to both tests six weeks after they had been inoculated in the bladder with tubercle bacilli.

Necker and Paschkis[19] report that the inoculation of animals has confirmed the value of the cutaneous reac-

14. Gaz. hebd. d. sc. méd. de Bordeaux, July 21, 1907.
15. Semaine méd., 1907, p. 585.
16. Acad. d. sc., May 27, June 17, 1907; Semaine méd., 1907, pp. 85, 309.
17. Deutsch. med. Wchnschr., 1908, No. 4.
18. Berl. klin. Wchnschr., March 16, 1907.
19. Wien. klin. Wchnschr., March 5, 1908.

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tion in tuberculosis of the genitourinary tract. In forty-two suspected cases of genitourinary tuberculosis in the human they had only one positive cutaneous reaction which was not substantiated by animal inoculation of urine. Notwithstanding the above favorable reports, a majority of the investigators have reported unsatisfactory results with these experiments. Arloing[20] observed in nineteen tuberculous animals (cats, goats, dogs, rabbits and guinea-pigs) a positive cutaneous reaction which could not be considered specific, however, because the identical reaction occurred in nine normal control animals.

Joannowics and Kapsammer[21] obtained negative results with both reactions in a large series of tuberculous guinea-pigs. Levi and Klopstock[22] did not obtain a positive conjunctival reaction in the series of tuberculous guinea-pigs and dogs. Vaccination of tuberculous guinea-pigs with from a 1 per cent. to a pure solution of tuberculin constantly gave negative results. One animal gave a positive conjunctival reaction and on postmortem no tuberculous lesion was found. One which had given a positive conjunctival reaction to a 1 per cent. solution was free of tuberculous lesions at autopsy. Wolff[23] did not produce positive reactions in tuberculous guinea-pigs or rabbits, although these animals gave positive reactions to the subcutaneous test. From these investigations one must infer that the results of this research have been so variable as not to aid the establishment of the specificity of these reactions.

POSITIVE TUBERCULOSIS.

Cutaneous Reaction.—In 500 cases of positive tuberculosis, in patients between the ages of 5 and 14 years, von Pirquet reports 88 per cent. positive and 12 per

20. Soc. de biol., June 22, 1907.
21. Berl. klin. Wchnschr., 1907, No. 45.
22. Berl. klin. Wchnschr., Feb. 3, 1908. Deutsch. klin. Wchnschr., No. 3, 1908.
23. Berl. klin. Wchnschr., Feb. 10, 1908.

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cent. negative reactions. In a series of 143 cases (Table 1), of patients of all ages compiled of seven different authors, 70 per cent. gave positive reactions and 30 per cent. negative. In our own investigations of 55 cases (Table 10) 31 or 56 per cent. of the patients gave positive reactions, and 24 or 44 per cent. negative. A majority of our patients were in the third stage.

Conjunctival Reaction.—Of 1,572 cases by 30 different authors (Table 5) selected from the literature, 86 per cent. of the patients gave positive and 14 per cent. negative reactions. Schroeder and Kaufman[24] (Table 9) from a collection of 971 cases report that the patients in 88.5 per cent. gave positive and in 11.5 per cent, negative reactions. Our own results (Table 10) in the positive tuberculous cases with the conjunctival reaction was that of 70 patients 52 or 74 per cent. were positive and 18 or 26 per cent. were negative. The majority of these patients also were in the third stage. Wolff[23] found 30 per cent. of the patients in the first and second stages of tuberculosis reacted negatively to the conjunctival test and 37 per cent. negatively to the cutaneous reaction. Heinemann reports six cases of patients in the first and second stages of tuberculosis and Levi[22] four cases of patients not in the advanced or cachectic stages of tuberculosis (one of the kidney, one of the prostate, two of the knee-joint), which gave negative reactions. Webster and Kilpatrick[25] report cases of patients with beginning tuberculosis which gave negative conjunctival reactions. Mentoux[26] obtained negative conjunctival reactions in ten positively tuberculous children in the first stages of disease, MacLennan[27] obtained negative reaction in early tuberculosis (patients with hip disease in good condition and in two patients with phthisis which reacted positively to 10 mg. of tubercu-

24. München. med. Wchnschr., Jan. 14, 1908.
25. Brit. Med. Jour., Dec. 7, 1907.
26. French Congress for Internal Medicine, Paris, München. med. Wchnschr., Jan. 14, 1908.
27. Brit. Med. Jour., Dec. 7, 1907.

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lin (O. T.) subcutaneously). Kleinberger[28] reports 7 negative and 2 doubtful reactions of 17 patients with not advanced tuberculosis.

SUSPECTED TUBERCULOSIS.

Cutaneous Reaction.—in a series of 23 cases of children von Pirquet[1] reports 5 positive and 18 negative reactions. The patients in the 5 positive cases proved to be tuberculous and 15 of the patients in the negative cases were found to be free from tuberculosis at necropsy. In 195 cases of five authors (Table 2) 55 per cent. of the patients reacted positively 44.5 per cent. negatively and in 0.5 per cent. the results were doubtful. In our own results (Table 11) of 55 patients with suspected tuberculosis other than pulmonary (arthritis, adenitis, peritonitis, meningitis, etc.) 30 or 55 per cent. reacted positively and 23 or 45 per cent. negatively. In 42 patients with clinical symptoms of pulmonary tuberculosis (Table 12) 28 or 67 per cent. reacted positively and 33 per cent. negatively.

Cutaneous Reaction.—In a series of 23 cases of chil- (Table 6) 48 per cent. of the patients reacted positively, 50 per cent. negatively and in 2 per cent. the reaction was doubtful. Schroeder and Kaufman[24] (Table 9) reported practically the same percentage, 51.4 per cent. positive and 48.6 per cent. negative. For our own results (Table 11) in 40 cases other than pulmonary 21 or 52 per cent. of the patients resulted positively and 19 or 48 per cent. negatively. Of 52 patients with the clinical symptoms of pulmonary tuberculosis 15 or 28 per cent. reacted positively and 38 or 72 per cent. negatively (Table 12).

OTHER DISEASES CLINICALLY NON-TUBERCULOUS.

Cutaneous Reaction.—Of 252 cases in the literature (Table 3) 15 per cent. of the patients reacted positively and 85 per cent. negatively. In our own results (Table

28. München. med. Wchnschr., Jan. 14, 1908.

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13) in 268 cases 149 or 56 per cent. of the patients resulted positively and 119 or 44 per cent. negatively.

Conjunctival Reaction.—From a total of 932 cases collected (Table 8) the reactions of the patients in 17 per cent. were positive and in 83 per cent. negative. Schroeder and Kaufman[24] (Table 9), on a basis of 627 cases, found the patients' reactions in 12.7 per cent. positive and in 87.3 per cent. negative. Our own results (Table 13), with 417 patients, gave 102 or 24 per cent. positive and 315 or 76 per cent. negative. Cohn[9] produced positive reactions in 38 per cent. of the cases of typhoid. Plehn[29] obtained positive reactions in 2 of 5 patients with typhoid, 2 of 5 patients with scarlet fever, 6 of 12 patients with articular rheumatism, 3 of 6 patients with acute bronchitis, and in 3 patients with enteritis. In none of these patients was there the slightest evidence of tuberculosis. In one case a pregnancy complicated with pleurisy a positive reaction occurred from a 1 per cent. solution, and in the other eye two weeks later a negative reaction occurred from a 2 per cent. solution. In a case of articular rheumatism the patient gave a positive reaction during the activity of the symptoms. The symptoms of rheumatism promptly subsided on the administration of salicylates, but two weeks later returned and, simultaneously, without installation, a marked conjunctival reaction recurred in the eye previously instilled. Reuschel[30] reports one case of a patient with leukemia (free from tuberculous lesions at autopsy), which gave a positive reaction. Blum[31] obtained 16 per cent. of positive reactions in non-tuberculous diseases. Fisen[32] observed positive reactions in 31 per cent. of various non-tuberculous infections. Serafini found that the ocular reaction

29. Deutsch. med Wchnschr., Feb. 20, 1908.
30. München. med Wchnschr., Feb. 25, 1908. Reuschel quotes a case of leukemia reported by Escherich[67] in which there was a marked reaction to an injection of 4 mg. tuberculin (O. T.).
31. München. med. Wchnschr., Jan. 14, 1908.
32. Beitr. z. Klin. d. Tuberk., viii, No. 4.

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is not conclusive in tuberculosis of the bone. The reaction was positive in certain gonorrheal, senile and other non-tuberculous articular affections.

CLINICALLY NORMAL INDIVIDUALS.

Cutaneous Reaction.—Of 181 cases selected from the literature (Table 4) 91 or 50.2 per cent. of the patients gave positive and 49.8 per cent. gave negative reactions. The patients were of all ages. Burnet[13] reports positive cutaneous reactions in non-tuberculous people. Kleinberger obtained positive reactions in 16.6 per cent. of normal individuals. Stadelman[33] obtained positive reactions in 50 per cent. of adults. Warfield[34] reports 7 positive reactions in apparently normal individuals (1 in a 7-months-old baby and 6 in adults). von Pirquet[1] has found that in individuals from 10 to 14 years of age 55 per cent. and in adults 90 per cent. reacted positively. Freer obtained 35 per cent. of positive reactions in patients between the ages of 10 and 15 and Mainini[35] obtained positive cutaneous reactions six times more frequently than conjunctival reactions.

Conjunctival Reaction.—Of 351 cases selected from the literature (Table 8) 11 per cent. gave positive reactions and 88 per cent. negative and 1 per cent. doubtful. Smithies and Walker[36] obtained negative reactions in 70 apparently normal individuals. Webster and Kilpatrick[25] observed two positive reactions in four normal individuals. Mentoux[26] produced positive reactions in 16 children in only 3 of whom was there a slight suspicion of tuberculosis clinically. Stadelmann[33] obtained positive reaction in 16 per cent. of normal individuals. Baldwin[8] obtained 16 positive reactions in 57 normal individuals or a percentage of 28.

Our own results of clinically normal individuals were

33. München. med. Wchnschr., Jan. 14. 1908.
34. The Journal A. M. A., Feb. 29, 1908, l, 687; Interstate Med. Jour., March, 1908.
35. München. med. Wchnschr., Dec. 17, 1907.
36. The Journal A. M. A., Jan. 25, 1908, l, 259.

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obtained from experiments on students of the St. Louis University. These students were apparently healthy and many of them were active athletes, such as football men. Of a total number of 90 patients (Table 14) subjected to these reactions 79 were given the cutaneous and 70 the conjunctival, the entire number not taking both reactions. Of 79 cutaneous reactions 41 or 51 per cent. were positive, 18 negative and 20 doubtful, or 49 per cent. negative or doubtful. In 70 of these the conjunctival reaction in 18 or 25.5 per cent. was positive, in 46 negative and in 6 doubtful, or 74.5 per cent., was negative or doubtful. In 63 of these students who voluntered to take both reactions at the same time, the following remarkable results were obtained: In 43 per cent. both reactions were negative or doubtful; in 19 per cent. both reactions were positive; in 33.3 per cent. the cutaneous was positive and conjunctival was negative; in 4 per cent. the cutaneous was negative and the conjunctival was positive; 57 per cent. reacted positively to either one or both of these reactions; 52 per cent. gave positive cutaneous, and 23 per cent. positive conjunctival reaction.

Of the students who gave positive reactions six gave histories of either having tuberculosis in the family or of exposure to tuberculosis. In over twenty who were examined no clinical evidence of tuberculosis could be demonstrated. Two of the students who gave positive conjunctival reactions had chronic conjunctivitis. In three of the students conjunctival reactions were produced which required treatment. In one case a marked phlyctenular conjunctivitis, and in another edema of the eye-lid with a severe conjunctivitis occurred.

SUMMARY.

We must agree with Smithies and Walker[36] that the failure of definite conclusions with regard to these reactions in the above cases is to a certain extent due to poor technic, difference in the tuberculin preparation,

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absence of more positive control than the clinical findings, indefinite standard of reactions and the presence of unknown conditions which modify or prevent these reactions. Whether or not all of the above difficulties will ever be satisfactorily overcome, from the present status of the accumulated report on these reactions in adults, we deduce the following marked inconstancy with regard to their value as diagnostic agents:

SUMMARY OF ALL CASES CONSIDERED.

CUTANEOUS REACTIONS.

	No. Cases.	Per c't. Pos.	Per c't. Neg.
I. PositiveTuberculosis.			
Seven authors (Table 1)	143	70	30
Engelbach and Shankland (Table 10)	55	56	44
II. Suspected Tuberculosis.			
Five authors (Table 2)	195	55	45
Engelbach and Shankland (Table 11)	190	61	39
III. Other Diseases.			
Five authors (Table 3)	252	15	85
Engelbach and Shankland (Table 13)	268	56	44
IV. Clinically Normal.			
Four authors (Table 4)	181	50	50
Kleinberger	...	17	83
Freer (10 to 15 years)	...	35	65
Stadelmann	...	50	50
Engelbach and Shankland (Table 14)	79	51	49
Pirquet (10 to 14 years)	...	55	45
Pirquet (Adults)	...	90	10

CONJUNCTIVAL REACTIONS.

	No. Cases.	Per c't. Pos.	Per c't. Neg.
I. PositiveTuberculosis.			
Thirty authors (Table 5)	1572	86	14
Schroeder and Kaufman (Table 9)	971	85.5	11.5
Engelbach and Shankland (Table 10)	70	74	26
II. Suspected Tuberculosis.			
Twenty-two authors (Table 6)	642	48	52
Schroeder and Kaufman (Table 9)	284	51	49
Engelbach and Shankland (Tables 11-12)	190	40	60
III. Other Diseases.			
Nineteen authors (Table 7)	932	17	83
Schroeder and Kaufman (Table 9)	627	13	87
Engelbach and Shankland (Table 13)	517	24	76
IV. Clinically Normal.			
Eight authors (Table 8)	351	11	89
Stadelmann	...	16	84
Engelbach and Shankland (Table 14)	79	25.5	74.5
Baldwin	70	28	72

In positive tuberculosis the negative cutaneous reactions have varied from 30 per cent. to 44 per cent., and the negative conjunctival reactions from 11.5 per cent. to 26 per cent. It has been conceded from the first that patients with advanced tuberculosis give

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negative reactions. The later reports, however, of Wolff, Levi, MacLennan, Kilpatrick, Klemperer and others prove that patients in the first and second stages of tuberculosis, in good condition, also frequently give both cutaneous and conjunctival negative reactions. Negative reactions in beginning tuberculosis have been reported in as high as 30 per cent. to 37 per cent. of the cases by Wolff.

In suspected tuberculosis there is a constant finding in the hands of different men of about 50 per cent. negative and 50 per cent. positive reactions. The positive reactions in these cases have varied from 40 per cent. to 48 per cent. with the conjunctival reaction, and 55 per cent. to 61 per cent. with the cutaneous reaction.

In other diseases not considered tuberculous clinically the percentage of positive reactions has varied from 15 per cent. to 56 per cent. with the cutaneous and from 13 per cent. to 24 per cent. with the conjunctival.

In clinically normal individuals there has been a wide range of difference with the positive reactions. These have ranged from 17 per cent. to 90 per cent. with the cutaneous reaction, and from 11 per cent. to 28 per cent. with the conjunctival reaction.

In comparing the table of cases selected from the literature one is struck with the same amount, practically, of positive reactions which occur in non-tuberculous diseases and clinically normal individuals. In comparing the suspected with the positive tuberculous case. compiled, the difference is not enough to warrant positive conclusions.

	Cutaneous.		Conjunctival	
	P.C. Pos.	P.C. Neg.	P.C. Pos.	P.C. Neg.
Positive Tuberculosis	56	43	74	26
Suspected Tuberculosis (not pulmonary)	55	45	52.5	47.
Suspected Tuberculosis (pulmonary)	67	33	28	72
Other Diseases (non-tuberculous clinically)	56.5	43.5	24	76
Clinically normal individuals	51	49	25.5	74.5

In our own work, which is shown in the above table, the cutaneous reaction in the five conditions (positive tuberculosis, 56 per cent.; suspected tuberculosis, not

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pulmonary, 55 per cent.; suspected pulmonary tuberculosis, 67 per cent.; other diseases, 56 per cent.; clinically normal individuals, 51 per cent.) was practically the same percentage. Our cases of positive conjunctival reaction in suspected pulmonary tuberculosis (28 per cent.) other diseases non-tuberculous clinically (24 per cent.) and clinically normal individuals (25.5 per cent.) also occurred practically in the same relative number of cases.

CLINICALLY NORMAL INDIVIDUALS SUBJECTED TO BOTH CUTANEOUS AND CONJUNCTIVAL REACTIONS.

	No.	Per Cent.
Individuals	63	..
Positive reactions	36	57
Positive cutaneous reactions	33	52
Positive conjunctival reactions	15	23
Positive cutaneous, negative or doubtful conjunctival	21	33
Positive conjunctival, negative or doubtful cutaneous	3	4

Furthermore, a perusal of the above table will demonstrate that these reactions are very variable in normal individuals, i.e., one reaction will be present in the absence of the other one without any definite relation or apparent cause for this variation. We have also observed this variance in known tuberculous cases and in other diseases not considered tuberculosis clinically.

LOCAL LESIONS OF THE EYE.

It has already been established that a number of diseases of the eye, tuberculous and non-tuberculous, will in themselves give positive reactions and absolutely interdict the use of the conjunctival reactions. These conditions of the eye necessarily restrict the use of this reaction in a high percentage of cases. The lesions of the eye may be so slight as to be entirely overlooked by those not especially skilled in the diagnosis of eye diseases. It is probable that in two of our normal cases in which the patients gave positive eye reactions, that this reaction was due entirely to a slight chronic conjunctivitis which was not observed previous to the instillation. The above facts probably account for many of the positive reactions which are credited to non-tuberculous diseases.

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Notwithstanding the concensus of opinion regarding the unreliability and the untoward effects produced by this reaction in abnormal eye conditions, a number of oculists have used it as a means of diagnosis in eye diseases. Maillet,[37] from its use in local diseases of the eye, says that he has not observed an unfavorable effect. In three positive cases of tuberculosis, each patient having a lesion in one eye, a positive reaction was produced in the diseased eye as well as the healthy eye by instilling the healthy eye. In all non-tuberculous eye diseases there was a negative reaction in both eyes. Tuberculous chorioiditis and trachoma were not affected unfavorably by this reaction.

Franke[38] reports that this reaction was of much value and entirely harmless in twenty-four cases of disease of the eye. Stephenson[39] believes that the conjunctival reaction has positive value in differentiating tuberculous from non-tuberculous eye affections, as confirmed by his experience in thirty cases. Among the diseases in which it is of special value he reports his personal observations on the following: Phlyctenular (eczematous) conjunctivitis and keratitis, chorioiditis, interstitial keratitis, episcleritis, tubercle of the iris, tubercle of cornea and chronic iridocyelitis. Painblan[40] obtained positive results in two cases of tuberculosis of the conjunctiva. Brunetiere[41] had no negative results in three cases thought possibly to be of tuberculous origin, keratoiritis, interstitial keratitis, and exudative chorioiditis. Aubaret and Lafon[42] employed the reaction in eighteen eye cases including intraocular tuberculosis, phlyctenular conjunctivitis and keratitis, interstitial keratitis, lachrymal affections and optic papillitis.

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37. Rev. gén. d'Ophth., Nov. 30, 1907.
38. Deutsch. med. Wchnschr., 1907, No. 48.
39. Brit. Med. Jour., Oct. 19, 1907. Ophthalmoscope, Dec. 1, 1907.
40. L'Opht. provinciale, August, 1907.
41. L'Opht. provinciale, August, September, 1907.
42. Gaz. hebd. d. sc. méd. de Bordeaux, Aug. 4, 1907.

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In contrast with the findings of the above men, Schiele,[43] Kraemer, Truc, [44] Souques,[45] Mery,[46] Schenck-Seiffert[47] and others show that local conditions of the eye, especially trachoma and granular conjunctivitis, give positive reactions without the presence of either a local or distant tubercular process. Schele[43] also maintains, however, that other conditions (chalazia, pterygia, chronic hyperemia, epiphera, subacute conjunctivitis) in non-tuberculous patients never give a positive reaction. He says this is a valuable aid to differentiate syphilitic from tuberculous keratitis. He emphasizes the fact that one might be misled in a case of healed trachoma without scars, which would in itself give a positive reaction. Brunetiere in the course of a second communication while reaffirming the diagnostic value of the reaction regretted that it could not be applied to every doubtful case. The following is a report by Dr. Clarence Loeb on positive eye reaction in our clinically normal individuals. It includes two cases of chronic conjunctivitis which we hold accountable for the reaction, and one case of phlyctenular conjunctivitis produced by this instillation.

CASE 1.—M. K., March 16, 1908.

Right Eye: Chronic dilatation of vessels of palpebral conjunctiva. Bulbar vessels normal.

Left Eye: Palpebral conjunctiva shows rough areas resembling granulation tissue on the lower fold of transmission. Otherwise injected. Bulbar conjunctiva about same as other side. Plica and caruncle slightly more injected than other side. Fundi normal and similar. Vision, both eyes, separately, 6:6.

CASE 2.—R. F., March 17, 1908.

Right Eye: Palpebral conjunctiva slightly hyperemic. Bulbar not. Vision, 6:6.

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43. Wchnschr. f. Therap. u. Hyg. d. Auges, Dec. 5, 1907.
44. Jour. de méd. et de chir., Jan. 10, 1908.
45. Jour. de méd. et de chir., Jan. 10, 1908.
46. Jour. de méd. et de chir., Jan. 10, 1908.
47. Jour. de méd. et de chir., Jan. 10, 1908; München med. Wchnschr., 1907, No. 46.

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Left Eye: Bulbar conjunctiva like other eye. Palpebral conjunctiva injected and shows enlargement of some of the follicles. Vision, 6:6. Both fundi normal. Caruncle and plica moderately injected.

CASE 3.—L. W. A., March 15, 1908.

Right Eye: Bulbar conjunctiva shows a few dilated vessels. Palpebral conjunctiva shows a slight chronic conjunctivitis. Region of the caruncle normal.

Left Eye: Bulbar conjunctiva shows a few dilated large vessels. Numerous smaller vessels appear, which are not visible in the other eye. The region of the caruncle is very red and the palpebral conjunctiva is much more injected than that of the other eye. The bulbar conjunctival injection is much more pronounced in the periphery gradually becoming less as the cornea is approached. Both fundi are normal. There is no apparent difference in the color of the discs or the size of the retinal vessels.

CASE 4.—J. F. R., March 15, 1908.

Right Eye: Slight injection of bulbar conjunctiva. Chronic dilatation of palpebral conjunctival vessels. Vision, 6:6.

Left Eye: Dilatation of smaller vessels of the bulbar conjunctiva, especially pronounced on the inner side, where they can be followed to the cornea. The deeper scleral vessels are also dilated posteriorly. The palpebral conjunctiva is markedly hyperemic and the caruncle and plica semilunaris are very red. A slight amount of crust is seen on the margin of the lids. Both discs are of normal color, perhaps slightly redder than normal. Blond fundus. The veins of the left fundus are possibly a trifle more dilated than those of the right. Vision, 6:6.

CASE 5.—C. B., March 15, 1908.

Right Eye: Palpebral conjunctiva shows chronically dilated vessels. Disc shows a physiologic excavation. Vision, 6:6.

Left Eye: Small amount of yellowish secretion in the conjunctival sac. The palpebral conjunctiva is very hyperemic. In the bulbar conjunctiva all around, but more pronounced internally, from behind forward, run small dilated vessels which do not reach the cornea. The plica and caruncle are very red. Disc shows a physiologic excavation. The veins of the left fundus are a trifle fuller than those of the right.

CASE 6.—O. A., March 17, 1908.

Right Eye: Practically normal. Vision, 6:8, with difficulty.

Left Eye: Conjunctiva palpebræ inferioris injected. In a semi-circle reaching from the internal margin of the horizontal

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meridian to the inferior margin of the vertical meridian are several small phlyctenules, to which run a group of small but dilated vessels. Both fundi normal.

THE SPECIFITY OF OTHER TOXINS.

In attempting to determine the specificity of tuberculin reactions it is necessary to consider the specific reactions of other toxins applied in this manner, especially those reactions produced or present in other diseases with tuberculin and the reactions produced in tuberculosis by other toxins. Schick[48] attempted to apply the cutaneous reactions in the diagnosis of diphtheria. In 22 patients not given diphtheria antitoxin, 18 reacted positively, 3 doubtfully and 1 negatively. The reaction was constantly negative when antitoxin was given in sufficient quantities. Positive reactions of less intensity occurred when antitoxin was given in insufficient amounts. He concluded that this reaction was of value in estimating the dose of antitoxin to be given in an individual case.

Ferrand and Lemaire[49] observed when using diphtheria toxin by vaccination according to von Pirquet's method, that it produced a positive reaction in tuberculous cases which differed from the tubercular reaction in being composed of an infiltration of polynuclear leucocytes. Link experimented with the cutaneous reaction with typhoid, paratyphoid and colon toxins on 14 patients (5 typhoid patients, 4 paratyphoid patients and 5 normal individuals). In some cases of typhoid he obtained a positive cutaneous reaction in individual patients with all three of the toxins. In two of the normal cases he procured positive reactions in the same case with two different toxins. Orsvag,[50] from his personal investigations, concluded that the cutaneous typhoid reaction was of no value.

48. München. med. Wchnschr., March 10, 1908.
49. München. med. Wchnschr., March 10, 1908.
50. Deutsch med. Wchnschr., April 9, 1908.

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Recently Chantemesse[51] communicated his discovery that 1/80 mg. of typhoid toxin in one drop of water instilled in the eye of a healthy individual produces only a slight conjunctival reaction which disappears in 4 to 5 hours. In active or convalescent cases of typhoid this reaction begins in from 6 to 12 hours, and lasts longer than 24 hours. A positive reaction is characterized by marked injection, lachrymation, and the presence of a serofibrinous exudate. He constantly produced positive reactions in rabbits which had been inoculated two days previous with typhoid bacilli.

Kraus,[52] from his results from instilling different toxins, concludes that the conjunctiva of individuals suffering from typhoid react not only to typhoid, but to paratyphoid, colon, tuberculin and probably other toxins. Kraus,[53] Lusenberger[54] and Russ[55] confirm the results of Chantemesse regarding the typhoid conjunctival reactions in so far as this reaction is present in typhoid and not in healthy individuals. They found, however, that this toxin was not specific for typhoid alone. They produced with it positive reactions in patients suffering from other diseases, tuberculosis, pneumonia, multiple sclerosis, etc. They also found that paratyphoid toxin caused no reaction in healthy individuals, but obtained seven positive reactions in thirteen typhoid patients with a paratyphoid toxin. Colon toxin also gave a negative reaction in healthy individuals, but gave positive reactions in all of the eleven typhoid patients instilled. Tuberculin caused a positive reaction in 11 of 12 typhoid patients who gave no clinical evidence of tuberculosis.

Orsvag[50] obtained positive reactions in the majority of typhoid cases after the first 24 hours, and says a negative reaction speaks against the probability of

51. Bull. Acad. de Méd., Paris, July 23, 1907.
52. Wien. klin. Wchnschr., No. 45, 1907.
53. Wien. klin. Wchnschr., Nov. 7, 1907.
54. Wien. klin. Wchnschr., Nov. 7, 1907.
55. Wien. klin. Wchnschr., Nov. 7, 1907.

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typhoid. Recurrences of typhoid reacted in 50 per cent. of the cases. In other diseases 50 per cent. of the reactions were negative, but positive reactions occurred so frequently in non-typhoid individuals as to make the specificity of this reaction questionable. Hamburger[56] reports constant positive conjunctival reactions in 27 typhoid patients instilled with typhoid toxins, and negative reactions in 15 patients with other diseases, and in 5 other patients probably not typhoid.

Our own observations with the use of typhoid toxins in known tuberculous cases and other diseases (Table 15) are as follows: We instilled 78 patients with this toxin. Of 48 positive tuberculous patients 8 reacted positively in the first 36 hours. Only 2 of these reactions remained positive after the first 36 hours. None of these patients gave a history of typhoid. Of the 29 patients with other diseases not tuberculous, 1 reacted markedly and 2 gave mild reactions after 24 hours. None of these three patients had had typhoid. Among these cases, however, were three typhoid patients, of whom one gave a negative, and 2 gave slight reactions after 36 hours. We used in this series of typhoid toxin instillation 1 per cent. and 2 per cent. toxin furnished us by the Alexander Laboratory. This laboratory did not recommend the toxin on account of having some difficulty in providing a reliable one which actually contained typhoid toxin. The difficulty has been encountered by Orsvag and others who claim it is impossible to obtain typhoid toxin for this use on account of the toxins of typhoid being endotoxins.

We are led to conclude from the above that toxin reactions in general have not proved specific for the following reasons: 1. Tuberculin gives positive reactions in cases of typhoid fever; 2, typhoid toxin reactions have been demonstrated positive in tuberculosis; 3, the different toxins, typhoid, paratyphoid, colon and tuberculin have given positive reactions in the same case.

56. The Journal A. M. A., April 25, 1908, l, 344.

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ACTIVITY OF THE LESION.

Believing that both of these reactions are specific ones for tuberculosis, Wolff-Eisner, Mainini,[35] Stadelmann[38] and others maintain that they also indicate the activity and the extent of the lesion. They believe that a positive cutaneous reaction with a negative conjunctival reaction on the first instillation with a positive conjunctival reaction on the second instillation indicates a latent tubercular lesion. A positive conjunctival reaction at the first instillation is indicative of an active tuberculous lesion. Wolff-Eisner and Teichmann[57] draw definite conclusions from the onset, intensity and the duration of the cutaneous reaction to the activity of the lesion and the prognosis of the case. They have described the following three types of the cutaneous reaction.

Type 1.—The reaction begins 4 to 6 hours after vaccination, reaches its greatest intensity in 20 to 24 hours, as an elevated papule, 10 to 20 mm. in diameter, continuing thus throughout the second day, and gradually disappearing during the third and fourth day to a slight pigmented area for the course of 3 or 4 weeks. There are two varieties of this type, the "marked" and the "moderate." This type is taken to indicate incipient tuberculosis, and first and second stage of tuberculosis, of non-progressive type with a favorable prognosis.

Type 2.—This is a slight reaction characterized by rapid course of mild intensity. It begins about the sixth hour, rapidly reaches its acme, sometimes in 10 hours, when it is from 4 to 10 mm. in diameter, and rapidly disappears not later than the second day without pigmentation. It is said to occur in the third stage of tuberculosis, and in the first and second stages of unfavorable cases having a bad prognosis.

Type 3.—This is a late prolonged reaction. It begins as the other types, reaches its greatest intensity 8 to 10

57. Berl. med. Wchnschr., Jan. 13, 1908.

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mm. in diameter at the end of the second day, and persists unchanged for at least a week. It is taken to indicate latent tuberculosis.

The conjunctival reaction they say occurs only in Types 1 and 2, in varying degrees of intensity. They conclude that the cutaneous reactions show marked differences in intensity in the various forms of tuberculosis, depending on the lysis of the bacilli-débris, and the effect on the body of the toxins set free.

In contending against the value of the diagnosis of the activity of the lesion, as claimed above, we wish to join those investigators who disagree with these authors for the following reasons: 1. Animal experimentations have not confirmed their findings; 2, positive tuberculosis of the first and second stages have given both the conjunctival and cutaneous reactions in an inconstant manner, a negative cutaneous reaction, or negative cutaneous reaction with a positive conjunctival reaction; 3, the clinical course of cases giving these reactions has not borne out their predictions; 4, not enough absolute postmortem control has been observed to substantiate their theory.

The animal experiments given in the beginning of this article, as was shown, did not even demonstrate these reactions as specific ones for tuberculosis. The reactions occurred in animals with such variance to the findings on autopsy that the relationship in animals of the reactions to the activity of the lesion needs no further comment. Baginsky[58] reports negative cutaneous reactions in a child in good general condition who reacted postively to 1/5 mg. tuberculin (O. T.) subcutaneously. Wolff,[28] Heinemann,[59] Levi,[22] MacLennan[27] and others have shown that negative reactions occur in the first and second stages of active, but not cachectic, tuberculosis. Webster and Kilpatrick[25] have demonstrated that the conjunctival reaction occurred in

58. Berl. med. Wchnschr., June 3, 1907.
59. München. med. Wchnschr., March 17, 1908.

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clinically quiescent and non-quiscent tuberculosis. Mentoux[26] has shown that negative conjunctival reactions occur in beginning active tuberculosis, and that positive recations were present in non-tuberculous children.

The clinical course on positive reactions has not borne out the prognostic value of the combined reactions as demonstrated by Heinemann,[59] who reports one case of tuberculous peritonitis which gave a negative reaction with a final recovery. He also reports a case of bilateral apical lesion which was treated for many months after negative reactions, and which gave later a positive reaction. Engel and Bauer[60] found 6 cases which gave positive cutaneous reactions, five of the patients were certainly free from tuberculosis, as proved in one case by postmortem, and in four cases by negative subcutaneous reaction.

Our own observations have demonstrated a marked variability of the occurrence and intensity of these reactions which we have not been able to explain upon the activity or extent of the lesion. The relationship of these reactions either in combination or the degree of intensity of the single reaction are so inconstant that we are inclined to believe with Reuschel[30] that the reactions demonstrate at most the presence of anti-tuberculous bodies and not tuberculosis. These antibodies depend more on the resistance of the body for their productions than the extent or activity of the infection. The variability of these reactions on this basis is consequently more easily explained. It is yet to be determined, however, whether the sensibility, demonstrated by these methods, is due to antibodies or to albuminous substanes in the serum.

PROGNOSTIC VALUE.

The prognostic as well as the diagnostic value of these reactions have been affirmed by the majority of the

60. Berl. klin. Wchnschr., No. 37, 1907.

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investigators as more or less certain. Some have even claimed that a negative reaction in known tuberculosis indicates a very unfavorable prognosis, death occurring in the majority of these cases within ten days. The same contention would apply to these tests as has been given above, i. e., the questionable specificity of these reactions and the inconstant relationship of the activity and extent of the lesions to the intensity of the reaction. The presence of negative reactions in non-progressive tuberculosis of the first and second stage, as demonstrated by Wolff, Heinemann, Levi, Phlen and Mentoux, and the presence of a positive conjunctival reaction with a negative cutaneous reaction in clinically normal individuals, argue against this claim for these reactions. The clinical course and postmortem findings of cases subjected to these reactions have not borne out this significance of these reactions. Known tuberculous patients have given negative reactions and then been observed for a long time or cured as reported by Heinemann,[59] Sabrazes, Duperes[14] and others.

DURATION OF LIFE AFTER REACTIONS IN POSITIVE TUBERCULOSIS.

Days from reaction to death.	Reactions.		Positive (26)	Negative (26)
1 to 10	pos.	7	*b, a, b, a, b, b, a*	*b, d, b, d, a, b*
	neg.	11	.....	*b, a, a, a*
10 to 20	pos.	5	*b, b, b, a, a*	*b, b, a, a, d, e*
	neg.	6	.....	.....
20 to 30	pos.	6	*b, b, b, b, b, c*	*a, d, e*
	neg.	3	.....	.....
40 to 50	pos.	3	*b, b, a,*	*a, b*
	neg.	2	.....	.....
After 50	pos.	5	*a* (120 days)	*b* (69 days)
			c (87 days)	*d* (59 days)
	neg.	4	*c* (71 days)	*e* (112 days)
			c (128 days)	*d* (83 days)
Total		52	*c* (68 days)	

(*a*, cutaneous reaction; *b*, conjunctival reaction; *c*, both reactions positive; *d*, both reactions negative; *e*, cutaneous reaction positive, and conjunctival negative.)

In our own work we had 52 patients who died after being subjected to these reactions (see above table). Twenty-six of the patients reacted positively and 26 negatively. Of those who died in the first ten days,

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after one or the other of these reactions, 7 reacted positively and 11 negatively. Of 11 patients who died in from 10 to 20 days after inoculation 5 reacted positively and 6 negatively. Ten patients died in from 20 to 30 days after inoculation, of whom 3 reacted negatively and 7 positively. Of 5 patients who died in from 40 to 50 days after inoculation, 3 reacted positively and 2 negatively. Nine patients lived for from 50 to 128 days after being inoculated; four of these reacted negatively and 5 positively. Three patients who were not considered tuberculous clinically, and on whom the postmortem findings were negative, gave positive reactions. One of these gave a positive cutaneous reaction 6 days before death. One gave a positive cutaneous and negative conjunctival reaction 67 days previous to death. One gave positive reactions to both tests 73 days before death.

From the above we conclude that in known tuberculosis the kind of reaction has no bearing on the prognosis of the case. Positive reactions have occurred with us as early as one day before death; both reactions have been present in variable percentage as long as three months previous to death. The negative reactions have practically equaled the positive reactions in occurrence two or three months previous to death.

UNTOWARD EFFECTS OF THE CONJUNCTIVAL REACTION.

The evidence of accumulating cases has unquestionably proven that the conjunctival instillation of tuberculin is not entirely free from danger. On the contrary, from the following report one must conclude that there is a liability of producing severe inflammatory processes in normal eyes, of aggravating non-tuberculous affections of the eye, and of producing an extension, and in some cases a rapidly destructive process, in tuberculous affections of the eye, from its use. McKay[61] reports

61. Boston Med. and Surg. Jour., March 12, 1908.

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a severe conjunctivitis lasting over ten weeks in an eye that was normal previous to the instillation of a 1 per cent. solution. Eppenstein[62] reports three cases of conjunctival phlyctenular keratitis which were greatly exaggerated, and says that chronic hyperemia, blepharitis or conjunctivitis of any kind contraindicates its use.

Ferrien[63] reports a conjunctivitis lasting two months, which terminated by having the aspects of tuberculosis of the conjunctiva. Babier and Renon[64] have observed conjunctivitis persist for one or two months. Stevenson reported three cases of follicular conjunctivitis which existed from 20 to 40 days. Kalt[65] reports serious result in iritis, sclerokeratitis and iridochorioiditis. Trousseau[66] reports a marked extension of a tubercle of the conjunctiva immediately following the instillation of a 0.5 per cent. of tuberculin. In another case a tuberculous iritis was greatly aggravated, although the reaction was negative. Babier[64] reports keratitis and ulceration of the cornea from a conjunctival reaction. A large majority of other authors, not oculists, have observed more or less unfavorable results varying in degree and severity from this test.

Besides these local untoward reactions Wolff[23] observed a very marked febrile reaction in the conjunctival test. Wolff-Eisner[57] and many others obtained general reactions. Proff noted that the tuberculo-opsonic index was modified by these reactions, and that in some cases the negative phase was marked and unusually prolonged.

COMPARISON OF THESE REACTIONS WITH THE SUBCUTANEOUS.

MacLennan[27] found that in 25 patients, of whom 14 were clinically tuberculous, 12 reacted positively to the

62. Med. Klin., Sept. 8, 1907.
63. Bull. Soc. d'Ophth. de Paris, Oct. 8, 1907.
64. Bull. et mém. Soc. d. hôpitaux de Paris, Dec. 12, 1907.
65. Bull. Soc. d'Ophth. de Paris, Oct. 8, 1907.
66. Jour. de méd. et de Chir., Jan. 10, 1908.

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subcutaneous and 10 to the conjunctival test. Baldwin[5] believes that these reactions correspond closely to the subcutaneous, which when given systematically to healthy and suspected individuals produce from 50 to 60 per cent. positive reactions. Wolff, in 27 patients with suspected tuberculosis, obtained 59 per cent. of positive cutaneous reactions, and 92 per cent. of positive subcutaneous reactions. In 45 patients the conjunctival reaction was positive in 29 per cent., and the subcutaneous reaction in 80 per cent. Moro,[6] in comparing the conjunctival with the inunction or percutaneous reaction, found that in suspected tuberculous patients 16 per cent. gave conjunctival and 17 per cent. the cutaneous reaction.

Reuschel[30] advocates the "puncture" reaction of Escherich as of much more value than either the cutaneous or the subcutaneous reaction. This reaction consists of a circumscribed red area of infiltration, edema, and pain surrounding the site of the subcutaneous puncture of the hypodermic injection. He found that this reaction was constant in cases of tuberculosis, which did not give the febrile reaction, and it was of special value in febrile cases. On the other hand, the febrile response to the subcutaneous injection of tuberculin in the absence of the puncture reaction was not regarded by him to indicate tuberculosis.

We wish to take this opportunity of expressing to senior house physicians, Dr. R. Bunch and Dr. F. Esselbruegge our appreciation for services rendered us in the preparation of this article.

CONCLUSIONS.

The diagnostic value of these reactions in adults is restricted to many limitations.

The specificity of these reactions have as yet not been demonstrated, as proven by: 1. Experimental work on animals; 2, the presence of a positive reaction in nontuberculous conditions; (a) local conditions of the eye,

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trachoma follicular conjunctivitis, etc.; (b) general conditions; clinically normal individuals, other diseases not tuberculous (typhoid) controlled clinically and by autopsy; 3, the presence of a negative reaction in tubercular cases, (a) miliary tuberculosis, tuberculous meningitis, advanced pulmonary tuberculosis, etc., (b) incipient and second stage tuberculosis controlled clinically and by autopsy; 4, the production of this reaction by other toxins, typhoid, etc., in tuberculous cases.

The activity or extent of the lesion bears no definite relation to the degree or kind of reaction, for: 1, One or both of these reactions have occurred in clinically normal individuals in an inconstant manner; 2, there is a marked variation of the occurrence of these reactions in different stages of clinical tuberculosis; 3, there has been no more definite control than the clinical findings of the relationship of the stage of the lesion with the degree and kind of reaction.

The conjunctival reaction is not free from danger, for: 1, Non-tuberculous lesions of the eye have been aggravated by it; 2, tuberculous lesions of the eye have been stimulated into activity by this reaction; 3, general or constitutional symptoms have been produced by this instillation.

(See following pages for tables.)

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TABLE 1.—CUTANEOUS REACTIONS.—POSITIVE TUBERCULOSIS.

Author.	No. of Cases.	Age.	Reaction.		Control Diagnosis.	Reaction.		Control Diagnosis.
			Pos.	Per Cent.		Neg.	Per Cent.	
1. Pirquet[1]	.....	5-14		88	.....	.....	12	
2. Olmer and Terres[10]	57	.....	20	.....	.....	11		
3. Baginsky[58]	1	Child	.....	.....	.....	1	.....	Pos. to 0.5 and 0.2 mg. sub.
4. Wolf[23]	19	17 adults, 2 child.	12	63.2	First and second stage	7	36.8	First and second stages.
5. Reuschel[30]	28	.....	10	.....	Tuberculosis, 7 cases, autopsy; 6 + and 1 − subcutaneous.	18	.....	20 of this number = + clinical findings and 8 were +.
	14	.....	14					
6. Necker and Paschkis[19]	19	.....	19	.....	Animal inoculation			
7. Bing[71]	19	.....	14	73.7	.....	5	26.3	
8. Warfield[34]	12	Adult	11	.....	.....	1		
	143	.....	100	70	.....	43	30	

67. Escherich: Jahrb. f. Kinderh., 1892, p. 419.
68. Piccard and Descomps: Bull. Soc. d. hôp. de Paris, June 27, 1907.
69. Dufour: Bull. Soc. d. hôp. de Paris, June 27, 1907.
70. Presse méd., Sept. 18, 1907.
71. Berl. klin. Wchnschr., March 16, 1908.

TABLE 2.—SUSPECTED TUBERCULOSIS.

Author.	No. of Cases.	Age.	Reaction.		Control Diagnosis.	Reaction.		Control Diagnosis.
			Pos.	Per Cent.		Neg.	Per Cent.	
1. Pirquet[1]	23	Child	5	.....	Autopsy +	18	.....	Autopsy, 15 negative.
2. Wolf[23]	90	5-13 23 adults.	47	52.2	27 of these suspect, 16 or 59.2 per cent. = + reaction; 25 or 92.5 per cent = +, 11 subcut. Pos. findings in 7 of above 27 by *x*-ray.	43	47.8	
3. Reuschel[30]	14	.....	14	.....	Pleuritis, serose, scrofula, clinical T. B. C.			
4. Bing[71]	36	.....	25	69	.....	11	31	
5. Warfield[34]	32	8-51	16	.....	.....	16		
Total	195	.....	107	55	.....	88	45	

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TABLE 3.

OTHER DISEASES, NON-TUBERCULAR.

Author.	No. cases.	Reaction. Pos.	Reaction. Per cent.	Control Diagnosis.	Reaction. Neg.	Reaction. Pr. ct.	Control Diagnosis.
1. Pirquet[1]	16	..	16				
2. Olmer & Terres[70]	17	3	..		14	..	
3. Reuschel [20]	8	..	.	Autopsy leukemia..	7	..	Autopsy subcutaneous.
	18	1	..		18	..	
4. Necker & Paschkis[19]	23	1	..	Animal inoculation.	22	..	Animal inoculation.
5. Bing[71]	186	34	18.2		152	81.8	
Total	252	39	15		213	85	

TABLE 4.

CLINICALLY NORMAL INDIVIDUALS.

Author.	No. cases.	Reaction. Pos.	Reaction. Per cent.	Control Diagnosis.	Reaction. Neg.	Reaction. Pr. ct.	Control Diagnosis.
1. Pirquet[1]	..	..	35		..	65	
	..	..	2		..	98	
2. Engel & Bauer[60]	48	6	..	1 cut. T. B. C. 4— to subcut. test. 1 + to subacut.test.	42	..	
3. Baginsky[68]	19	12	..		7	..	
4. Warfield[84]	55	54	..		1	..	Mother T. B. C. Neg. to 5 and 10 mg. T. O. subcutan.
	51	15	..	Reacted to 1 mg. T. O. subcutaneous.	36	..	
	1	1	..				
	1	..	..		1	..	
	6	3	..		3	..	
Total	181	91	50		90	50	

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TABLE 5.

CONJUNCTIVAL REACTIONS.

POSITIVE TUBERCULAS.

Author.	No. cases.	Reaction. Pos.	Reaction. Per cent.	Control Diagnosis.	Reaction. Neg.	Reaction. Pr. ct.	Control Diagnosis.
1. MacLennan[27]	25	23	..		2		
2. Kohler[72]	169	161	51		8	49	
3. Maillet[67]	4	4			..	4.7	8% + to 4% O. T. 41% + to 2% O. T.
4. Plehn[30] (see article)	38	31	81.6		7	18.4	
5. Cohn[9]	86	60	2	3 not in terminal stage.	26	2	
6. Colzolari[73]	12	3	..		9		
7. Wolff[23]	20	14	70	18 adults, 2 children.	6	30	Early 2d stage tubercular.
8. Webster & Kilpatrick[36]	43	43					
9. Letulle[74]	75	72	..		3		
10. Grasset & Rumdand[75]	7	7			1		
	1						
11. Proff	13	13					
12. Smithers & Walker[36]	29	20	..	1 after 1 and 5 mg. T. O. 1 slight after 1 1 mg. T. O. 2 marked after 1mg. T. O. 1 after 1, 5 and 10 mg. T. O.			
13. Baldwin[8]	53	50	..		3	..	1 miliary tuberculin; 1 tuberculin treated.
14. Schenck & Seiffert[47]	28	27	..		1		
15. Lenhartz	37	33	..		4	..	4 tuberculin treated.
16. Citron[79]	31	25	..		6		
17. Eppenstein[62]	85	60	..		25		
18. Mentoux [26]	15	14	..		1		

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19. Schroeder & Kaufman[24]	48	43	..		5		
20. Franke & Ratjen	6	6					
21. Andeoud[76]	13	12	..		1		
22. Blumel-Clarus[77]	289	260	..		29		
23. Calmette, Breton, Petit, Painblan and other authors[80]	111	108	..		3		
24. Comby[78] (children)	62	62	..	Clinical and autopsy 4 +			
25. Bing[71]	6	3	50		3	50	
26. Citron[79]	36	70	81	+ without cachexia.	16	19	
	14	2	14.4	+ with cachexia....	12	85.6	
	15	14	93	+ not tubercular...	1	7	
27. Mentoux[26]	10	..	..	Children, 1st stage.	10		
28. Moro[3]	8	5	..	Percut. react. +7..	3	..	Percut. react.—1. Percut. react. —1. Percut. react.—3.
	12	12	..	Percut. react. 11 2d.			
	4	1	..	Percut. react. 1 3d.			
29. Heinemann[50] (1st, 2d, 3d)	25	20	..	1 case tubercular peritonitis, recovery; 1 case treated many months for cilat. lesion gave — reac. later.	..	..	3 cases init. hemorrhage.
	18	18	..				
	5	2	..		3		
30. Levi[22]	69	45	66		18	..	14 advanced; 4 not advanced or cachetic; 1 unilteral tuberculous kidney; 1 tubercular prostate; 1 T. B. C. knee.
Total	1,572	1,352	86		214	14	

72. Deutsch. med. Wchnschr., 1907, No. 50.
73. Riforma medica., July 26, 1907.
74. Bull. Soc. d. hôp. de Paris, Aug. 31, 1907.
75. Bull. Soc. d. hôp. de Paris, Aug. 31, 1907.
76. Bull. méd. 1907, xi, No. 20.
77. Med. Klin., 1907, No. 50.
78. Presse méd., 1907, No. 10.
79. Sitz. d. Berl. med. Gesellsch., July 24, 1907; Deutsch. med. Wchnschr., Feb. 20, 1908.
80. Compt. rend. Acad. d. Sc., July 7; la Presse méd., July 13, 1907, No. 56.

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TABLE 6.

SUSPECTED TUBERCULAR.

Author.	No. cases.	Reaction. Pos.	Reaction. Per cent.	Control Diagnosis.	Reaction. Neg.	Reaction. Pr. ct.	Control Diagnosis.
1. MacLennan[27]	12	9	..		3	..	Clin. 1 tubercular hip 2 yrs. +2 react.
	12	10	..		2	..	10 mg. T. O. subcutaneous.
	20	19	..		1	..	Anim. inoc. sacral abscess.
2. Kohler[73]	5	2	..				
	..	3	..				
3. Cohn[9]	32	23	..		9	..	Not all negative to subcutaneous.
4. Wolff[23]	64	20	39.2	14 child. 50 adults. 80 to subcut.	43	61.2	
5. Webster & Kilpatrick[25]	58	36	..	Phys. Ex. +.....	18	18	Phys. ex. + .1 mg. O. T. bacilli in sputum 1 month previous.
	16	6	..	Phys. Ex. ?.....	7	7	Phys. ex. ?
6. Grasset & Rumdand[75]	5	5					
	3				3		
7. Proff	6	..	..		6	..	Babies born; tubercular mother.
8. Smithers & Walker[26]	6	6					
9. Baldwin[5]	26	8	..	Clinical	14	..	Clinical.
10. Schenck & Seiffert[47]	20	6	30	No positive physical findings.			No positive physical findings.
	..	6	30				
	..	3	15		5	25	
11. Lenhartz	63	23	..		40		
12. Citron[79]	14	11	..		3		
13. Eppenstein[62]	89	38	..		51		
14. Metraux	11	9	..		2		
15. Schroeder & Kaufmann[24]	9	4	..		5		
16. Franke & Ratjen	12	9	..		3		
17. Andeoud[76]	3	1	..		2		
18. Comby[78] (children)	70	..	..		70	..	Clinically, 6 autopsy.
19. Bing[71]	15	6	..		9		
19. Ctron[79]	18	10	55.5	Clinicl	8	44.5	
20. Mentoux[36]	3	3	..	Clinical			
21. Moro[8]	17	10	..	Percut. +16	7	..	Percut. react. — 1.
22. Heineman[50]	33	22	..		11		
Total	642	308	48		334	52	

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TABLE 7.

OTHER DISEASES NON-TUBERCULAR.

Author.	No. cases.	Reaction. Pos.	Reaction. Per cent.	Control Diagnosis.	Reaction. Neg.	Reaction. Pr. ct.	Control Diagnosis.
1. MacLennan [27]	20	4	..		16		
2. Maillet[37]	4	4	..				
3. Pihen[39]	5	2	..	Typhoid, acute articular rheumatism, acute bronchitis, scarlet fever, enteritis, pleurisy and pregnacy, rheumatism, reaction reappeared with return of rheumatism.	3		Typhoid, acute articular rheumatism, acute bronchiti, scarlet fever, pleuritis and pregnancy two weeks later.
	12	6	..		6		
	6	3	..		3		
	5	2	..		3		
	3	3	..				
	1	1	..		1		
	1	1	..				
4. Cohn[9]	192	10	..		182		
5. Calzolari[73]	19	..	..		19		
6. Letulle[74]	50	19	..		31		
7. Grasset & Rumdand[75]	14	..	..		14		
	1	1	..				
8. Smithers & Walker[46]	136	10	..		126		
9. Baldwin[8]	57	16	..	Clinical	41	..	Clinical.
10. Schenck & Seiffert[47]	52	3	57				
	..	11	22		26		Clinical.
	..	12	23	Clinical			
11. Citron[79]	45	1	..		44		
12. Eppenstein[48]	13	4	..		9		
13. Mentoux[80]	42	2	..		40		
14. Schoreder & Kaufman[34]	20	12	..		8		
15. Franke & Ratjen	33	4	..		29		
16. Andeoud[76]	15	..	..		15		
17. Calmette, Breton, Painblan, Petit and other French authors[50]	87	1	..		86		
18. Moro[5]	25	6	..	Per cut. + 8	19		
19. Heinemann[49]	63	10	..		53		
Total	932	152	17		779	83	

TABLE 8.

CLINICALLY NORMAL INDIVIDUALS.

Author.	No. cases.	Reaction. Pos.	Reaction. Per cent.	Control Diagnosis.	Reaction. Neg.	Reaction. Pr. ct.	Control Diagnosis.
1. Mailliet[38]	15	..	..		15		
2. Webster & Kilpatrick[38]	4	2	..		2		
3. Proff	17	..	..		17		
4. Smithers & Walker[36]	76	2	..		74		
5. Baldwin[8]	47	16	..	Not all physicians' findings	30		One reacted to a 2 per cent. solution which had been — to 10 mg. T. 0.
6. Bing[71]	79	1	1.2		78	98.8	
7. Citron[79]	100	6	6	Clinical	..	...	
8. Mentoux[36]	13	13	..	Clinical	..	...	
Total	351	40	11		311	89	

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TABLE 9.

TABLE OF SCHROEDER AND KAUFMANN.

Author.	Positive Tuberculosis. No.	Pos.	Neg.	Suspected Tuberculosis. No.	Pos.	Neg.	Non-Tuberculous. No.	Pos.	Neg.
Lenhartz	38	33	4	63	23	40	11	4	7
Cohn	86	60	26	3	23	9	192	10	182
Citron	31	25	6	14	11	3	45	1	44
Kohler	169	161	8	5	5	..	..	..	..
Eppenstein ...	85	60	25	89	38	51	13	4	69
Baldwin	53	50	3	26	8	18	57	16	41
Metraux	15	14	1	11	9	2	42	2	40
Schenck-Seyffert	28	27	1	20	15	5	52	26	26
Andeoud	13	12	1	3	1	2	15	..	15
BlumelClarus..	289	260	29	..	..	..	..	..	..
Calmette u. a. franz. authors	111	108	3	..	..	..	87	1	86
Schroeder-Kaufmann	48	43	5	9	4	5	20	12	8
						(Nor)	18	12	6
Franke-Ratjen..	6	6	..	12	9	3	33	4	29
Total	971	859	112	284	146	138	627	80	547
Per cent.		88.5	11.5		51.4	48.6		12.7	87.3

TABLE 10.

CASES OF ENGELBACH AND SHANKLAND.

POSITIVE TUBERCULOSIS.

	Positive No.	Per cent.	Negative No.	Per cent.	Total.
Cutaneous	31	56.4	24	43.6	55
Conjunctival	52	74.3	18	25.7	70
Total	83	66.4	42	33.6	125

TABLE 11.

SUSPECTED TUBERCULOSIS (OTHER THAN PULMONARY.)

	Positive No.	Per cent.	Negative No.	Per cent.	Total.
Cutaneous	30	55	25	45	55
Conjunctival	21	52.5	19	47.5	40
Total	51	54	44	46	95

TABLE 12.

CLINICALLY PULMONARY TUBERCULOSIS.

	Positive No.	Per cent.	Negative No.	Per cent.	Total.
Cutaneous	28	66.66	14	33.3	42
Conjunctival	15	28	38	72	53
Total	43	47	52	53	95

TABLE 13.

OTHER DISEASES NON-TUBERCULOUS CLINICALLY.

	Positive No.	Per cent.	Negative No.	Per cent.	Total.
Cutaneous	149	56.5	119	43.5	268
Conjunctival	102	24.4	315	75.6	417
Total	251	36.6	434	63.4	685

TABLE 14.

CLINICALLY NORMAL INDIVIDUALS.

	Positive No.	P.C.	Negative No.	P.C.	Doubtful No.	P.C.	Total.
Cutaneous ...	41	51	18	22.8	20	25.3	79
Conjunctival...	18	25.5	46	65.8	6	8.6	70
Total	59	38	64	44.3	26	16.9	149

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TABLE 15.

OTHER DISEASES NON-TUBERCULOUS CLINICALLY (IN DETAIL).

Diseases.	Reactions.	Pos.	Neg.	Total.
Aneurisms	Cutaneous	..	..	..
	Conjunctival	..	3	3
Abscesses	Cutaneous	1	..	..
	Conjunctival	3	4	8
Arthritis	Cutaneous	3	..	..
	Conjunctival	..	..	3
Asthma	Cutaneous	1	3	..
	Conjunctival	1	4	9
Amputations	Cutaneous	1	1	..
	Conjunctival	..	1	3
Appendicitis	Cutaneous	1	1	..
	Conjunctival	..	1	3
Abortion	Cutaneous	..	..	..
	Conjunctival	..	5	5
Alcoholism	Cutaneous	3	..	..
	Conjunctival	3	5	11
Burns	Cutaneous	1	1	..
	Conjunctival	2	3	7
Bronchitis	Cutaneous	8	10	..
	Conjunctival	9	13	40
Cirrhosis	Cutaneous	1	1	..
	Conjunctival	1	1	4
Carcinoma	Cutaneous	2	..	..
	Conjunctival	2	2	6
Contusions	Cutaneous	1	..	..
	Conjunctival	..	2	3
Colitis	Cutaneous	1	..	..
	Conjunctival	..	..	1
Cellulitis	Cutaneous	1	1	..
	Conjunctival	..	1	3
Choleangitis	Cutaneous	..	..	..
	Conjunctival	..	2	2
Cerebral Hemorrhage	Cutaneous	2	2	..
	Conjunctival	..	3	7
Cholelithiasis	Cutaneous	..	..	..
	Conjunctival	1	1	2
Diphtheria	Cutaneous	..	4	..
	Conjunctival	..	..	4
Dementia	Cutaneous	1	1	..
	Conjunctival	3	2	7
Dislocations	Cutaneous	..	..	..
	Conjunctival	1	2	3
Epilepsy	Cutaneous	..	..	..
	Conjunctival	1	5	6
Empyema	Cutaneous	..	..	..
	Conjunctival	..	..	2
Erysipelas	Cutaneous	7	4	..
	Conjunctival	1	4	16
Fever, Scarlet	Cutaneous	1	1	..
	Conjunctival	..	..	2
Fever, Typhoid	Cutaneous	1	1	..
	Conjunctival	1	2	5
Fractures	Cutaneous	15	8	..
	Conjunctival	6	21	50
Fistula	Cutaneous	..	..	..
	Conjunctival	..	2	2
Gunshot wounds	Cutaneous	..	1	..
	Conjunctival	..	4	5

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Diseases.	Reactions.	Pos.	Neg.	Total.
Gastritis	Cutaneous	1	..	..
	Conjunctival	2	5	8
Hysteria	Cutaneous	..	..	..
	Conjunctival	..	2	2
Hernia	Cutaneous	1	..	..
	Conjunctival	1	5	..
Hemiplegia	Cutaneous	5	2	..
	Conjunctival	..	4	11
Influenza	Cutaneous	1	..	..
	Conjunctival	3	2	6
Infections	Cutaneous	4	4	..
	Conjunctival	..	3	11
Lumbago	Cutaneous	..	1	..
	Conjunctival	..	2	2
Myocarditis	Cutaneous	..	1	..
	Conjunctival	..	1	2
Measles	Cutaneous	1	2	..
	Conjunctival	..	..	3
Morphinism	Cutaneous	1	..	..
	Conjunctival	..	5	6
Malaria	Cutaneous	1	2	..
	Conjunctival	..	4	7
Pneumonia	Cutaneous	2	8	..
	Conjunctival	8	24	42
Plumbism	Cutaneous	3	2	..
	Conjunctival	4	6	15
Paralysis	Cutaneous	1	1	..
	Conjunctival	2	2	6
Pleurisy	Cutaneous	..	2	..
	Conjunctival	1	5	8
Poisoning, Carbolic, etc.	Cutaneous	..	..	..
	Conjunctival	..	4	4
Regurgitation, Mitral	Cutaneous	11	6	..
	Conjunctival	5	25	47
Rheumatism	Cutaneous	12	6	..
	Conjunctival	17	38	73
Nephritis	Cutaneous	11	11	..
	Conjunctival	3	18	43
Necrosis	Cutaneous	1	1	..
	Conjunctival	..	1	3
Otitis Media	Cutaneous	..	..	..
	Conjunctival	2	1	3
Salpingitis	Cutaneous	1	..	..
	Conjunctival	..	3	4
Sensility	Cutaneous	7	5	..
	Conjunctival	..	6	18
Sprains	Cutaneous	..	2	..
	Conjunctival	..	..	2
Syphilis	Cutaneous	25	10	..
	Conjunctival	6	15	56
Stricture	Cutaneous	..	2	..
	Conjunctival	1	3	6
Tonsillitis	Cutaneous	1	1	..
	Conjunctival	1	4	7
Tables Dorsalis	Cutaneous	6	1	..
	Conjunctival	1	2	10
Ulcers	Cutaneous	..	3	..
	Conjunctival	2	7	12
Varicella	Cutaneous	1	1	..
	Conjunctival	..	..	2
Miscellaneous	Cutaneous	4	6	..
	Conjunctival	7	24	41

(In above table all doubtful reactions are counted negative.)

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TABLE 16.—TYPHOID SERUM REACTIONS IN POSITIVE TUBERCULOSIS.

Name.	Diagnosis.	Age.	Per cent. sol.	Eye.	Condition of Eye.	Physical Condition.	Time and Reaction.				History of Typhoid.
							12 hrs.	24 hrs.	36 hrs.	48 hrs.	
J. K....	Tbc.	39	2	L.	Good....	Good..	+	+	+	+	Negative.
L. M...	"	47	2	L.	Slight..	Fair..	—	—	—	—	"
C. M...	"	44	2	L.	Good....	Fair..	—	—	—	—	"
C. S...	"	30	2	L.	Slight..	Fair..	—	—	—	—	"
D. R...	"	52	2	R.	Slight..	Poor..	—	—	—	—	"
H. S...	"	53	2	L.	Rt. eye red lid.	Fair..	—	—	—	—	"
A. K...	"	48	2	L.	Gran. lids.	Fair..	—	—	—	—	"
L. W..	"	42	2	L.	Good....	Fair..	+	+	+	+	"
W. S...	"	38	2	L.	Good....	Fair..	—	—	—	—	"
W. R..	"	22	2	L.	Good....	Fair..	—	—	—	—	"
E. W..	"	73	2	L.	Slight...	Poor..	—	—	—	—	"
J. W...	"	36	2	L.	Slight...	Poor..	—	—	—	—	"
B. C...	"	50	2	R.	Slight...	Poor..	—	—	—	—	"
J. C...	"	48	2	L.	Slight...	Poor..	—	—	—	—	"
K.....	"	55	2	L.	Slight...	Poor..	—	—	—	—	"
J. K...	"	50	2	R.	Slight...	Poor..	—	—	—	—	"
P.....	"	17	2	L.	Slight...	V. pr..	—	—	—	—	"
M. C...	"	57	2	L.	Slight...	V. pr..	—	—	—	—	Pos. at 30 yrs. age.
R. B...	"	44	2	L.	Slight, rt. eye.	Fair..	—	—	—	—	Negative.
F. T..	"	55	2	L.	Slight, rt. eye.	Poor..	—	—	—	—	"
P. W...	"	29	2	R.	Slight...	Poor..	—	—	—	—	"
C. B...	"	32	2	R.	Slight...	Poor..	—	—	—	—	"
J. W...	"	29	2	L.	Slight...	Poor..	—	—	—	—	"
G.....	"	55	2	R.	Slight...	Poor..	—	—	—	—	"
J. R...	"	38	2	L.	B. slt...	Poor..	—	—	—	—	"
T. B...	"	54		R.	B. slt...	Poor..	—	—	—	—	"
V.....	"	54	2	R.	Slight...	Poor..	+	+	+	+	"
H.....	"	26	2	L.	Slight...	Poor..	—	—	—	—	"
S.....	"	39	2	R.	Slight...	Poor..	—	—	—	—	"
G.....	"	42	2	L.	L. slt...	Poor..	—	—	—	—	"
H. C...	"	42	2	R.	B. OK..	Poor..	—	—	—	—	Pos. at 16 yrs. age.
G.....	"	55	2	R.	Slight...	Poor..	—	—	—	—	Negative.
W. R..	"	22	2	R.	Good....	Poor..	—	—	—	—	"
M. G...	"	42	1	R.	Good....	Fair..	+	—	+	+	"
W. S..	"	40	1	R.	Good....	Fair..	—	+	—	—	"
A.....	"	49	1	L.	Good....	Fair..	—	—	—	—	"
S.....	"	....	1	L.	Good....	Poor..	—	—	—	—	"
H.....	"	50	1	L.	Good....	Poor..	—	—	—	—	"
C.....	"	50	1	R.	Good....	Poor..	—	—	—	—	"
S.....	"	45	1	R.	Good....	Pr. M.	+	—	+	+	"
J. S...	"	50	1	R.	Good....	Poor..	—	+	—	—	"
H.....	"	26	1	R.	Good....	Poor..	—	—	—	—	"
P.....	"	17	1	R.	Good....	Poor..	+	—	+	+	"
M. C..	"	57	1	R.	Good....	Poor..	+	+	—	—	"
B.....	"	....	1	R.	Good....	Poor..	—	—	—	—	"
B.....	"	32	2	R.	Good....	Poor..	—	—	—	—	"
W.....	"	31	2	R.	Good....	Pr. sl.	+	—	+	+	"
G.....	"	55	2	R.	Good....	Pr. sl.	+	+ +	+	+	"

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DISCUSSION.

Dr. Gerald Bertram Webb, Colorado Springs: Dr. Arnold Klebs, of Chicago, who was to open the discussion of this paper, has been detained by a committee meeting and has asked me to state his position in regard to the tuberculin reactions. Dr. Klebs agrees with the gentleman who wrote the paper in almost every detail. He feels that the specificity of the reactions had not been positively demonstrated. For diagnosis he prefers the well-tried subcutaneous tuberculin test, but he thinks it should be kept in the hands of experts and not used indiscriminately, and even then all other methods of diagnosis should first be exhausted. Of the integumental tuberculin tests Dr. Klebs prefers the cutaneous test of von Pirquet, which, he thinks, might also be interpreted as having some prognostic value. I myself think that by means of these reactions it is perhaps possible to substantiate in the living what the German proverb has long suggested regarding the dead. I disapprove the tendency to the present widespread and general use of these tests, for I consider their interpretation difficult and think that they might develop considerable phthisiophobia. Of the integumental tests I prefer the Moro inunction, with which I have had fair success in 135 cases. I think it might be of use to detect early tuberculous foci which are aglow, as with me patients cured of tuberculosis have not reacted. I feel that few of the human race escape tuberculosis and that these tests may but strengthen this supposition.

Dr. H. Bascom Weaver, Asheville, N. C.: In the paper I read the day before, I stated that we should not use these tests until all other means have been exhausted. In the very doubtful cases we then should use reliable methods of diagnosis. There are two points brought out in the paper which I consider of great importance and of practical application. One is the fact that the conjunctival tuberculin test is not free of danger. We all know from the experience of thousands of physicians and clinicians the world over that the cutaneous tuberculin test is free of danger. The statistics alone would now convince us that there is no danger to be encountered in using the hypodermic injections of tuberculin for the purpose of making a diagnosis in cases of tuberculosis.

Dr. Frank Smithies, Ann Arbor, Mich.: My colleague, Captain Walker, and I have made more than five hundred instillations to date with various preparations of tuberculin. The work was begun with the idea of checking the reported work of French observers. The results obtained with the first preparations worked with agreed in the main with those of Calmette and his followers. In no case of moderately early pulmonary or bone tuberculosis did Captain Walker and I fail to secure positive conjunctival changes. With later preparations of "ophthalmo-tuberculin" the results have not been

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so uniform, but have approached the gross results tabulated by German observers. We consider that properly manufactured preparations for use in the eye are difficult to obtain in this country, and we place little confidence in the "ophthalmic discs" which were sent out by commercial houses. In cases of moderately advanced pulmonary tuberculosis we have secured positive evidence in 75.6 per cent.; in late stage cases eye changes were noted in 59.5 per cent., while 15 per cent. showed suspicious alterations in the conjunctivæ. In 205 cases not clinically diagnosed tuberculous, but 6.8 per cent. gave eye changes. Frequently in anemic or arteriosclerotic patients, reddening of the conjunctivæ is not evidence of reaction. In these cases there are frequently markedly increased lachrymation, mucopurulent exudate, with smarting sensations along the lid margins. In such instances in which the reaction is dubious it might be of value to examine some of the exudate microscopically for the presence of polynuclear leucocytes, as suggested by Lafite, Dupont and Molinier. I had expected that Dr. Shankland would say more about the question of frequent instillations. From the experience of Captain Walker and myself it appears to be quite possible to produce conjunctival changes in people who are not manifestly tuberculous. This seems especially probable after the tenth day, and frequently after the fifth day, when the instillations are made in the same eye. Captain Walker and I have made it a rule not to make the second instillation in the eye first instilled. I deplore the fact that there has been such indiscriminate use of tuberculin in the conjunctival sacs, perhaps largely due to commercial influences. I have personally observed cases in which children and grown persons have been subjected to several instillations of from 4 to 10 per cent. strengths of solution in the endeavor of the attendant to produce reaction where tuberculous foci were suspected. From my experience I am quite sure that in hospitals and dispensaries not sufficient care is taken of the eyes after instillation, and particularly so when positive manifestations are secured. If the eyes are not protected, severe conjunctivitis may readily result. I have seen no case of serious eye disturbance in which the eyes have been negative before instillation. I believe that, properly administered, the conjunctival tuberculin test is of great value as confirmatory evidence, but, as is the case with every other form of tuberculin test, can never take the place of careful physical examination of patients.

Dr. John M. Swan, Philadelphia: I hesitate to report the results we have had with the ocular tuberculin reaction at the Polyclinic in Philadelphia, because of the small number of cases. After using the test in nineteen cases, a severe corneal ulceration developed in one of the patients which nearly cost

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the child her eye. We then abandoned the test. Through the kindness of Dr. Eshner we were able to use this method in nineteen cases at the Polyclinic Hospital. Out of these, thirteen were negative and six were positive. Of the positive cases, two patients had suspicious signs at the apex, brought out by physical examination, and one had tuberculous arthritis of the hip. In the other three cases there were no discoverable signs of tuberculosis. We came to the conclusion that the ocular tuberculin test is not superior to the hypodermic administration of tuberculin for diagnostic purposes, and that in some cases it was dangerous.

Dr. Frederick T. Lord, Boston: In some experiments with the conjunctival test on guinea-pigs at the Massachusetts General Hospital, the full strength of old tuberculin was used. The experience in animals was in favor of the specificity of the test. All of eleven animals inoculated with the tubercle bacillus and tested at intervals showed the reaction at some period of the disease, while in twenty-five control animals, without tuberculosis, there was no response.

Dr. Hugo A. Freund, Detroit: It is interesting to observe how popular certain diagnostic methods become at times. I believe that eight months ago every county and state society in the country heralded the Calmette reaction with tuberculin as a useful diagnostic sign. To-day many hesitate in accepting it as a valuable diagnostic means in the general diagnosis of tuberculosis. One can do harm if the conditions were not watched with care. Dr. Smithies, of Ann Arbor, has spoken of the "second" reaction. This reaction usually comes on in a period varying from eight to ten hours and almost invariably after the first instillation in any subject. This is due to the sensitization of the eye. The first instillation causes an increased susceptibility to further instillations of drops of Calmette's tuberculin. The danger comes from this; not only does one get more marked reactions, but in most of the dangerous cases the instillations have been given after one physician had applied the test, the next physician not knowing this. I know of two instances in which the test gave bad results; in one there was a severe hemorrhage, and in the other a corneal ulcer was produced. The second physician made his solution and dropped it on the conjunctiva without asking the patient whether or not the first physician had used Calmette drops. In this way dangers may arise from the use of the ocular tuberculin test. This is a point which should be borne in mind.

Dr. George Douglas Head, Minneapolis, Minn.: I desire to speak about my personal experience with the subcutaneous method, although I have used the ocular tuberculin test in thirty or forty cases. In the last ten years I have injected Koch's tuberculin in about 135 cases, and in this experience

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many interesting observations have been made. In the first place I have discovered some ill effects. I recall one case of Addison's disease in a young woman who died thirty-six hours after the injection of tuberculin. This was an early experience. I admit that the dose of tuberculin given in that case was larger than the dose used at the present time. Therefore, this case, I believe, should be excluded from my statistics. I have also observed that in the late or old cases the use of tuberculin does positive harm when used for diagnostic purposes. I have noticed that in some of the advanced cases no reaction is obtained to the test at all, even though it has been proved that tuberculosis is present by an examination of the feces, the urine and other excreta, as well as the sputum. I have also noticed this fact, which had not been mentioned in the literature, so far as I know; namely, that some remarkable cures resulted from but one injection of tuberculin given for diagnostic purposes. I recall two such instances. I do not believe that the tuberculin test should be used in Addison's disease for diagnostic purposes. Cases resulting fatally have been noted in the literature. In the 135 cases inoculated 50 per cent. reacted to the tuberculin. This is a refutation of the argument that a majority of the people in this country have tuberculosis, since in this series only suspected cases were inoculated. It seems to me that we as medical men should recognize the fact that we are not diagnosing tuberculosis in the early stages. When we wait for the tubercle bacilli to appear in the sputum, when we wait for the physical signs to appear showing the site of the lesion, when we wait for the lesion to become so extensive as to be detected by the ordinary physical method, then we are waiting, in many cases, too long to be of any real service to our patient. I urge the use of the old tuberculin, subcutaneously in the early cases, for diagnostic purposes. When a patient comes to him with a little cough, with a normal or slight rise in temperature, with no evidence of the disease in the chest, I can not conscientiously say to such a patient, "You have tuberculosis," or "You have not tuberculosis." The way to determine whether such a patient has a tuberculous lesion in his body is to give tuberculin. If one uses the tuberculin and obtains a positive reaction, then the patient should be placed under proper surroundings for cure, even though no positive physical signs of the disease can be detected.

Dr. William Engelbach, St. Louis: These reactions, thought until a short time ago to be definite, simple and specific ones for tuberculosis, have produced a wonderful amount of work, as shown by the literature of recent date. On account of the simplicity of the test and optimistic favorable results reported, many physicians have been led to try them, and consequently the tests have been subjected to much misuse. The

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real object of our article was, first, to demonstrate the danger of the conjunctival reaction, and, second, to bring out the unreliability of both tests. These limitations should prevent the indiscriminate use of these reactions. I agree with all those who have discussed the paper that there is considerable danger in the use of the conjunctival reaction. The reaction of von Pirquet is absolutely harmless, but whether it has any positive value as a diagnostic agent in adults is problematic. Our own results show that in the five types of cases we procured practically the same percentage of positive cutaneous reactions, averaging about 50 per cent. in each. In the positive tuberculous cases 40 per cent. gave negative cutaneous reactions. In the suspected tuberculous cases our own results agree with those of other authors in averaging about 50 per cent. of positive reactions. von Pirquet himself reported in one communication 90 per cent. of positive cutaneous reactions in unselected cases of adults. For these reasons I believe that this reaction is of no value in adults. These facts do not, however, discredit the value of the cutaneous reaction in children. I do not agree with Dr. Weaver's statement about the subcutaneous reaction being free from danger. The reports of cases of sudden death and miliary tuberculosis resulting from these subcutaneous injections of tuberculin would contradict this. Some of the latter cases (miliary tuberculosis) resulted from a latent or quiescent tubercular lesion which probably had been stimulated into activity by the subcutaneous injection. The idea had occurred to us that the cutaneous reaction might be of value in controlling the indications for and the dosage of the subcutaneous injections. With regard to the technic, we used, and obtained practically the same results from, the various preparations of tuberculin made in this country and France. For the instillations in the conjunctival test we used preferably a 1 and 2 per cent. solution of old tuberculin in a boric acid normal saline solution. In no case have we used more than one instillation. This reduced our positive reactions to the minimum, for these positive reactions would no doubt have been very much higher had we instilled the opposite eye with the same or a stronger solution of tuberculin. We have done experiments on animals. The work of other men, however, has proved the results of these experiments to be variable. Some have inoculated tuberculous guinea-pigs with a pure solution of tuberculin, for instance, with negative reactions. In suspected tuberculous cases the positive conjunctival reactions agree with the results obtained with the subcutaneous reaction in these cases (20 to 25 per cent.), whereas the cutaneous (50 per cent.) is almost double the amount of the positive subcutaneous reactions. Besides the unreliability of von Pirquet's cutaneous reaction as a specific sign for tuberculosis, it is

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misleading, because it occurs in such a high percentage of apparently normal individuals and in those affected with other non-tuberculous diseases. This reaction, if unsubstantiated, would not only have a tendency to create a pthisiphobia, but also would produce false diagnosis, causing many patients with non-tuberculous diseases to be treated for tuberculosis. In suspected cases in which a positive cutaneous reaction is obtained, then the patient should be given the benefit of the doubt of being non-tuberculous until this reaction is confirmed by other findings. Much harm may come from the indiscriminate use of these reactions.

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A CASE OF SYPHILITIC INFECTION OF FOURTEEN YEARS' DURATION WITH PROTRACTED AND UNUSUAL FEBRILE SYMPTOMS.

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History.—Mrs. X., aged 36, was first seen July 5, 1907. Her father died at 40, of typhoid; her mother was still in good health, at 68. She has two brothers and one sister, in good health, One sister died of tuberculosis at the age of 26. The patient had had the usual diseases of childhood, but no other serious illness. Menstruation began at 14 and had been regular and painless. She had been married ten years, but never pregnant. In 1893 while visiting in another state she was supposed to have contracted malaria. The altitude of the locality in which she visited is about 1,200 feet, and not surrounded by swamps, and malaria has never existed there so far as can be learned. On returning home in 1893 she had a great deal of fever, occurring in attacks of one week or more duration, the temperature often reaching 103 or 104 F. as nearly as could be learned from imperfect records and the statement of the patient and her friends, the fever was continuous and not attended by any marked chills. She became emaciated and extremely weak and had a very irritable stomach. From this extreme condition she gradually improved, but was not in good health. She married in 1897. For the first few months of her married life her health remained about as in the previous four years. She then began to have chills and fever, which would reach 103 or 104 F. During the last five years she has been attended by many physicians who had made numerous diagnoses, the most frequent being that of malaria, then followed tuberculosis, ovarian tumor, gallstones and nephritis. For the malaria she received immense quantities of quinin, both by mouth and hypodermatically. The blood was repeatedly examined and no plasmodium found, except that it was alleged to have been found in a specimen of blood which the patient's husband obtained and forwarded by

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mail to the physician who examined it. This was in 1906. In 1896 the patient had "muscular trouble of the eyes," as she stated, but no authentic record could be found of the true condition of the eyes at that time. Syphilis was denied by the husband.

Examination.—The patient's weight was 96 pounds; pulse, 100; temperature, 102 F., at 5 p. m. Examining the heart the apex beat was found in the sixth intercostal space, one inch external to the mammillary line. There was deep cardiac dulness at the lower border of the third rib in the parasternal line; the right border of this dulness was slightly to the right of the left sternal margin. A slight inconstant systolic murmur was heard at the apex. The palpable arteries were sclerosed, but the blood pressure was not increased. The lungs were normal. The liver showed dulness in the parasternal line on the border of the sixth rib. The organ could be palpated about one inch below the border of the ribs. The edge was rounded and at one point felt uneven. On the left side, beneath the border of the rib, a mass of firm consistency, but regular in outline, could be palpated, extending three inches below the border of the ribs. I was first in doubt as to whether I was palpating spleen or kidney, but later decided the mass to be spleen. Examination of the pelvis was negative. There was no cutaneous eruption or scars, nor any lymphatic glandular enlargement. The pupils reacted normally and the abdominal, patellar and tendoachillis reflexes were normal. The Romberg sign was absent and cutaneous sensation was normal. Urinalysis was negative. Examination of the blood showed: Erythrocytes, 4,920,000; leucocytes, 10,937; hemoglobin, 70 per cent.; lymphocytes, small, 9 per cent.; transitional and large, 8 per cent.; polymorphonuclear neutrophiles, 82 per cent.; eosinophiles, 1 per cent. The red cells were slightly pale, in shape and size normal. No parasites of any kind were found. There were present a chronic interstitial hepatitis, a chronic interstitial splenitis, arteritis of the larger arteries and enlargement of the heart without increased blood pressure, showing that the enlargement of the heart was not secondary to the vascular changes and that the enlargement of the organs mentioned was due to a general infection, and not to chronic cardiovascular disease. The diagnosis of syphilis was made.

Treatment.—I immediately began specific treatment, using twenty-five injections. After the first ten days she had no more fever and began to improve. At the completion of the twenty-five injections, Dec. 1, 1907, she weighed 108 pounds. She then took potassium iodid in five-grain doses three times daily for one month. From Jan. 1, 1908, until March 1, 1908, she was practically without medicine and able to attend the theater

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and receptions, which she had not done in several years. On March 1, 1908, I began a second course of mercurial injections and completed by May 30 twenty-four injections.

Subsequent Examination.—On May 30, 1908, the patient's weight was 115 pounds. The apex beat was in the fifth intercostal space, slightly outside the mammillary line. Deep cardiac dulness began on the fourth rib and on the left sternal margin. The edge of the liver could be palpated on deep inspiration only. The mass formerly felt extending below the left border of the ribs had disappeared. Only a normal splenic dulness was obtainable. I received the following additional history: In the summer of 1893, when the patient was supposed to have malaria she had a breaking out on the legs and palms of the hands, which was scaly in character.

On March 14, 1908, the husband consulted me and I found syphilitic trouble of the rectum.

To my mind, the chief point of interest in the case is the persistency and duration of the fever which, in my experience, has not been characteristic of syphilitic infection. Had there been the slightest doubt of the correctness of the original diagnosis of syphilis it has been absolutely dispelled by the results of the treatment.

DISCUSSION.

Dr. Joseph L. Miller, Chicago: A few years ago I reported six cases of tertiary lues, all with elevated temperatures, and since then I have seen two more cases. The type of the fever is not always alike. In many patients it resembles malaria—an intermittent fever characterized by periodic attacks, with a daily rise in temperature, sweats, etc., and then a long period of freedom from the fever. In other patients there occurs a continuous fever of moderate degree of intensity. Then there is another type of continuous fever of high degree. Some of these cases have been diagnosed as cholecystitis because, at the same time with the fever, there were associatd attacks of pain over the gall-bladder region. Two cases I saw diagnosed as pulmonary tuberculosis because of an accompanying bronchitis. In two other patients no diagnosis had been made. In these patients, with one exception, there was a moderate leucocytosis of 10,000 to 12,000. The last patient seen and diagnosed at autopsy had a leucocyte count of 8,000. In some patients there was a marked diminution in the number of leucocytes, a leucopenia, while in others there was a normal count. One patient I saw had a continuous fever for sixty days, ranging from 102 to 105, and with absolutely no pain anywhere. Specific infection was suspected, but the patient

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denied it and there were no external evidences of the disease. Specific treatment was not given. There was a point of interest in this case: When the patient had had an elevated temperature for thirty days he received two injections of atoxyl of one grain each; this was given with nothing especial in view except the idea that it might modify the infection. Following these injections occurred profuse sweating, the temperature dropped to normal and remained normal or subnormal for two or three days, then it ran up again, remaining up until the fatal termination occurred in a few weeks. I did not necessarily associate this drop in the temperature with the atoxyl, for the patient received only two injections.

Dr. William J. Butler, Chicago: There is probobly no infection capable of producing a greater variety of clinical pictures so obscure, etiologically, as syphilis. Hitherto it has been the habit to teach that, in any case in which the diagnosis is not clear, in which the physician is not able to decide whether the patient has syphilis or not, the therapeutic test should be used in order to determine this point. The therapy test has not proved entirely satisfactory. During the past two years, however, a valuable means of diagnosis in syphilis, namely, the serum test, has been placed at the command of the profession, but its importance has not yet been fully appreciated. The reliability of the test had been proved beyond a doubt by the statistics collected within the past two years. In from 90 to 95 per cent. of the cases of syphilis with manifestations a positive reaction will result. In my cases of metasyphilitic or parasyphilitic diseases, 70 to 75 per cent. gave positive reactions. The case of visceral syphilis described by Dr. Buswell is representative of a class of cases in which the reaction is invaluable for diagnosis.

Dr. Charles G. Stockton, Buffalo: I believe the paper to be a very important one because it emphasizes a point which seems not to have been generally recognized, namely, that in late syphilis it is possible to have a continued fever, or intermittent fever, long continued, which does not go on to recovery under ordinary treatment, but which responds promptly under antisyphilitic treatment. I have seen cases without the usual manifestations of late syphilis, that is, cases in which the ordinary signs of a late syphilis were conspicuously absent. In one case in particular there was great difficulty in making a diagnosis; the diagnosis was made eventually by exclusion and by the therapeutic test. Similar experiences have been reported by Janeway, Musser and others. In addition to and substantiation of what Dr. Buswell has reported, much of value can be had from the literature.

Dr. William S. Thayer, Baltimore: The fever occasionally met with in late syphilis may be confounded with that of typhoid; I recall one particular instance. The patient had a

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continuous fever, irregular, perhaps more so than usual in typhoid fever. A diagnosis of typhoid was made. After the patient had been at least three weeks in the ward, on a careful examination a fusiform enlargement of one clavicle was detected. Under antiluetic treatment the patient made a rapid recovery. Since that time I have seen several cases. One of these in particular suggested typhoid fever in its course. It is important to bear in mind the possibility of syphilis as a cause of an unexplained fever.

Dr. C. F. Hoover, Cleveland: I have had several striking cases of fever occurring late in syphilis, and two of these I wish to report briefly. The first was the case of a patient, 30 years old, who suffered severe abdominal pain. She was operated on for appendicitis, but the surgeon failed to find the appendix. The patient had a temperature of 106. The abdomen was promptly closed. The next day the fever continued. After that time the fever persisted, ranging from 101 to 106; this kept up for six weeks; then mercurial inunctions were given, with a cessation of the fever and other symptoms. It was later proven that the patient had had a syphilitic infection five years previously. The second case was one of a severe phlebitis. One physician who saw the patient made a positive diagnosis of suppurative phlebitis consequent on appendicitis. A second physician who was called in suspected a syphilitic infection. This patient had violent rigors, a high range of temperature, etc. The symptoms all subsided promptly under mercurial inunctions.

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THE VISCOSITY OF THE BLOOD;

ITS VALUE IN CLINICAL MEDICINE.

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The peripheral resistance to the circulation of the blood is important in general pathology. On the degree of this resistance depends the cardiac energy required to maintain the circulation, as well as the tension of the circulating fluid, with its far-reaching influences on nutrition. Two factors dominate and control this resistance in accordance with well recognized physical laws. These factors are (1) the changing caliber of the arterioles, (2) the chemico-physical characters of the blood. That the first is much the more important there can be no doubt; but that the second, as indicated by its viscosity, is entitled to careful study will be evident on the slightest examination. Huerthle, for instance, calculated that the work done by the heart of the dog is more than four times as great as it would be if the blood vessels were filled with distilled water instead of blood. This difference is due to its viscosity, which is four and seven-tenths times that of water. In the human subject it is slightly greater, the average, according to Hirsch and Beck,[1] being 5.1.

There is not entire agreement among different observers as to the average normal viscosity of human

1. Muenchener med. Wchnschr., 1900, xlvii, 1685; Deutsches Arch. f. klin. med., Leipzig, lxix, 503; Id., lxxii, 560; Arch. f. exper. Path. u. Pharmakol., Leipzig, liv, 54. The following references may also be consulted: Burton-Opitz, R.: Am. Med., Phila., 1900, vii, 111; Jour. Exp. Med., 1906, viii, 59 and 240; Abstr. Am. Med., N. S., i, 42; Arch. f. d. ges. Physiol., cxii, 189.

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blood. Determann[2] found it 4.7 in man and 4.5 in women, and Ewart[3] even less. Kottmann, on the other hand, makes it 5.11, agreeing with Hirsch and Beck. My own observations, covering a considerable number of cases make it a little less than five. Physiologic variations are constantly occurring, and their limits are not yet definitely established. It appears to me that variations below 4.5 and above 5.5, if persistent, may well be regarded as abnormal.

Under pathologic conditions the viscosity has been found to vary from three to nine times that of distilled water. Such variations in the internal friction and cohesion of the blood must have a tremendous effect on the physics of the circulation; while the diagnostic and therapeutic problems suggested are of the first importance.

The volume of any fluid which will pass through a capillary tube, under given conditions is entirely dependent on its viscosity, and if the co-efficient of viscosity is known, can be calculated with mathematical exactness. Such a calculation, however, expressing the viscosity in absolute terms is obviously neither necessary nor practical for clinical medicine. As scientific physicians, however, we should understand the general principles on which these calculations are based, and these I will therefore briefly outline.

The factors which influence the rate of flow are the diameter and length of the capillary tube, the pressure applied to the fluid, and, finally, its viscosity. The smaller the diameter of the capillary tube the greater, relatively to the moving volume of fluid, becomes the surface in contact with the wall of the tube. The friction between these surfaces is one of the greatest obstacles to be overcome. Molecules of fluid in actual contact with the wall of the tube probably remain sta-

2. Verhandl. d. Congr. f. innere Med., Wiesb., xx, 476; Ztschr. f. klin. Med., lix, 283.
3. Brit. Med. Jour., Lond., ii, supplement, p. 10.

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tionary, and the flow is entirely due to the intromolecular motion of the fluid, the rate of flow increasing toward the center of the moving column. Hence, the larger the lumen of the tube, the greater will be the velocity of the center of the moving stream, which means not only a greater absolute flow, but a greater flow relatively to the size of the tube. In this way the changing caliber of the arterioles influences the velocity and consequently the volume of blood flowing through them.

It is furthermore obvious that the longer the capillary tube of a given dimension the greater will be the friction. The length of the tube is, therefore, an important factor.

The rate of flow will also be directly influenced by its pressure. Under normal conditions blood flows through the arterioles under a pressure equal to that exerted by a column of mercury from 100 to 125 mm. in height. Other conditions remaining the same, the rate of flow will bear a certain definite ratio to the pressure.

Finally, the rate of flow of the fluid will be less the greater its viscosity. Viscosity is a physical property dependent on the freedom of motion between the molecules or particles which constitute the fluid. As in the case of blood, the fluid may hold in suspension solid particles (corpuscles) which will greatly influence the viscosity. Heubner calculated that two-thirds to three-fourths of the viscosity of the blood is due to the corpuscles. In some of the current literature the viscosity of the blood is expressed in absolute terms derived from calculations based on the data just given. Different mathematical formulas, based on Poisseules law, have been used for this purpose.

As Ostwald's[4] physico-chemical measurements form the basis of most of the work along this line, I will quote the one used by him.

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4. Oswald: Physicochemical Measurements.

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The volume of liquid, v, flowing from a long capillary tube is $v = \frac{xpr\ t}{8cl'}$, where x is 3.1416, p the pressure, r the radius, l the length of the tube, all expressed in millimeters, and t, the time, expressed in seconds; c is a factor depending on the nature of the liquid and on the temperature, and is called the co-efficient of viscosity. It is consequently found by means of the equation, $c = \frac{xpr\ t}{8vl'}$, and is given in the absolute metric system if the pressure is expressed in ergs x cm.—3, the radius and length in cm., the volume in cc., and the time in seconds.

Such calculations as these are obviously too technical for clinical use, and are not at all necessary for the purposes of clinical medicine. What is needed is, first, some convenient uniform standard of comparison which will express the relative viscosity, and available at all times and places; and, second, a method for determining viscosity sufficiently simple in its character to make it practicable for routine examinations.

Such a standard is found in distilled water, and nearly all the work which has been done up to this time expresses the viscosity of the blood as so many times that of distilled water, even though giving along with it the results of the technical calculations above referred to which express it in absolute terms.

The original investigations by Poiseuille, dealing with the viscosity of the blood were made with defibrinated blood. While having a scientific interest, this method involves such a wide departure from physiologic conditions as to be devoid of clinical interest. Huerthle was the first investigator to use the uncoagulated blood of the lower animal. To Hirsch and Beck, however, belong the credit of making a practical application of the data and methods of Huerthle and preceding investigators to the requirements of clinical medicine. Their apparatus which was subsequently modified by Determann, Bence[5] and others is

5. Ztschr. f. klin. Med., Berl., lviii, 203.

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shown in Figure 1. It consists of a glass jar 4x7 inches and 10 inches high, which contains the measuring apparatus (1) attached to the standard by a clamp. The purpose of this jar is to immerse the apparatus in water at 38 C. so that the temperature conditions will not change during the observation. The measuring apparatus consists of the bent tube (2), the lower portion of which, including the ampulla (3), is filled with blood at (4) by removing the closed tube (5). The blood is drawn by suction through the capillary tube to the upper X, and is forced back by a uniform pressure to the lower X, the time required for traveling this distance under given conditions of pressure, temperature, etc., constituting the basis for comparison in making the necessary calculations.

Instead of using water Hirsch and Beck used freshly distilled anilin oil, the viscosity of which is known, but this requires a second calculation to reduce it to the standard of distilled water. The pressure, which is positive and not negative, as in my own method and that of Hess, is produced by the bulb (6) acting through the flask (7) and is regulated by the manometer (8). A tube of calcium chlorid is interposed to dehydrate the air before it comes in contact with the blood. Their observations are made under a uniform pressure of 450 mm. of benzol equal to 400 of water. It will be noted that this pressure does not even distantly approximate the physiologic pressure maintained in the circulating mammalian blood vessels. This usually exceeds 100 mm. of mercury, which would be equivalent to about 1,350 mm. of water.

The apparatus and method is too cumbersome and technical to fulfill the requirements above indicated, and after a little experience with it I set about to simplify the method. Absolute scientific accuracy is not required in any clinical investigation of this sort. Determann admits a possible technical variation of two-tenths to five-tenths of a second with the same appa-

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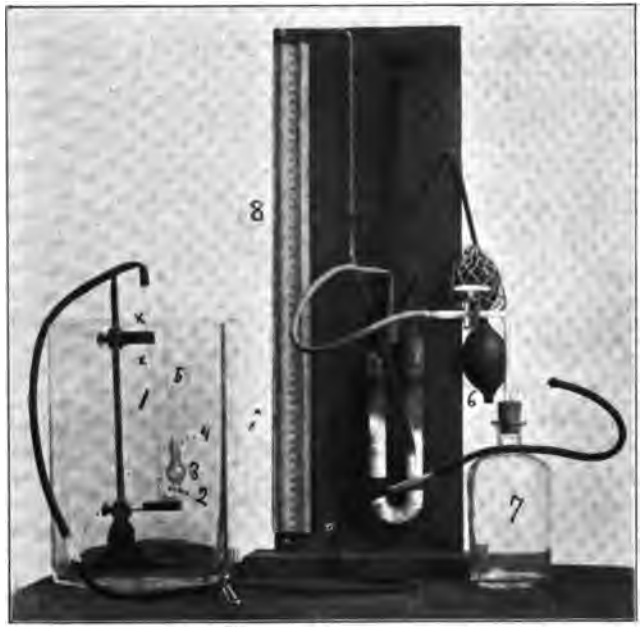

Fig. 1.—Hirsch and Beck's viscosity apparatus as modified by Determann, Bence and others.

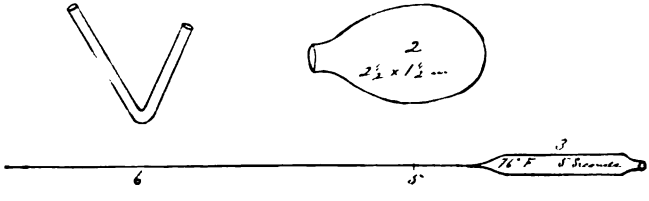

Fig. 2.—The author's viscosity apparatus.

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ratus, same blood and the same operator. It is largely a question of accuracy of co-ordinating two distinct movements at the same instant of time, and it requires considerable practice to avoid an error of a considerable fraction of a second. Furthermore the physical condition of the blood and therefore its viscosity is undergoing constant fluctuations depending on the amount of food and liquid absorbed, perspiration, urinary secretions and probably many other factors, concerning some of which we know little or nothing. Approximate results easily and quickly attained were therefore the objects in view.

The principle of forcing the blood through a given length of a capillary tube under definite pressure and temperature conditions and comparing the time with that which it takes to force distilled water through the same tube under the same conditions appeared to be the only fundamental requisites. The exact size of the capillary tube is not important, and really varied considerably in the appliances used by Hirsch and Beck, Ewart, Determann and others. Poiseulle, for instance, used tubes varying from .139 to .659 mm. and Hirsch and Beck tubes were from .25 to .35 mm.

As a result of my investigation I am now using the very simple appliance[6] shown in Fig. 2.

It consists of a capillary pipette (3) made from a piece of glass tubing with a lumen of 5 mm. One end is tapered (4) so that the rubber bulb (2) can be fitted over it easily. The other end is drawn out into a fine capillary tube, the exact size of which must be determined by experience. This is substantially the same as the capillary pipette used in opsonic work. A convenient length for the capillary portion of the tube is about six inches, and it should be made so that distilled water will pass through it under the negative pressure of the bulb in about five or six seconds. A blue pencil, or, much

6. This is much simpler than the apparatus that I showed at the Chicago meeting, as I have been able to eliminate the T-shaped glass tube with rubber tubing and clamp, which makes it less cumbersome.

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better, a fine ink mark is made at (5) just before the lumen of the capillary tube begins to enlarge, and each experiment terminates at the moment when the moving column reaches this mark.

The first thing to do is to "standardize" the tube with distilled water which constitutes the unit of comparison. The rubber bulb (2) is taken between the thumb and index finger of the right hand and compressed until its inner surfaces are in contact. It is important that this technic should be accurately followed. If this is done, there will not be any substantial variation in the negative pressure of the same bulb in different experiments. If, however, the bulb is compressed flatly between, say, the palmar surfaces of the thumb and two fingers, the pressure will be increased from forty to fifty per cent. and the results entirely vitiated.

The precise negative pressure will vary with different bulbs. With the one that I am working with, which measures 1½ x 2½ inches and is taken from a 10 c.c. volumetric pipette in my clinical laboratory, it is equal, approximately, to 50 mm. of mercury. Within reasonable limits the exact pressure is unimportant, so that it is the same with the blood that it was with the distilled water.

This bulb thus compressed is fitted over the capillary pipette at (4) and the pressure released. Air flows into the capillary tube under a constant negative pressure. With a stop-watch in the other hand, the end of the pipette is immersed in distilled water contained in a watch crystal and the stop-watch started at the same instant. The watch is stopped when the column of water reaches the mark at (5). This is repeated three or four times, and if there is any variation the mean of the several observations is taken and a label attached to the tube showing the result and also the temperature of the room.

The temperature of the room is important because the viscosity falls about two per cent. with each degree

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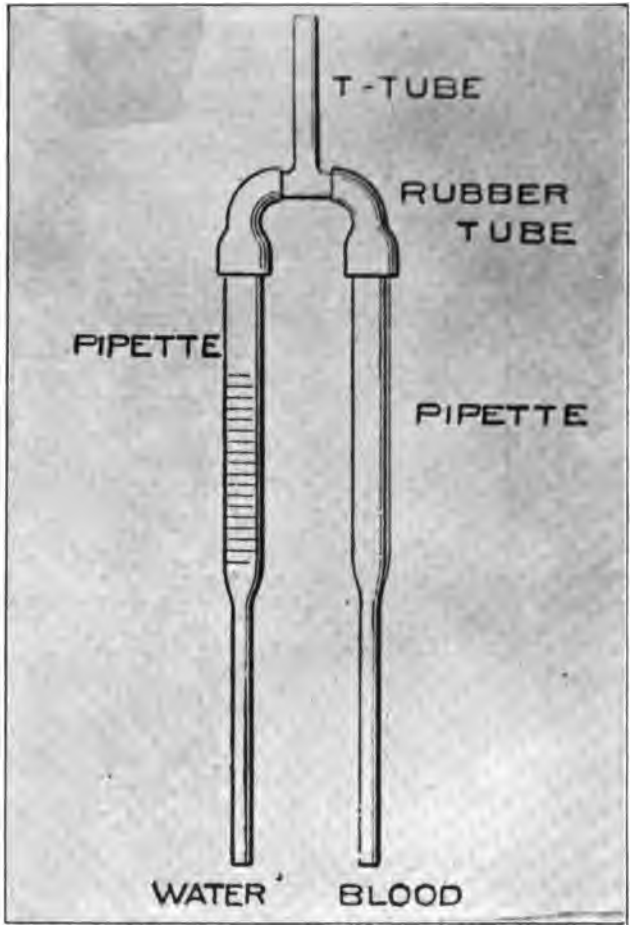

Fig. 3.—Hess' viscosity apparatus.

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centigrade of rise of temperature, and if the observation on the blood is made at a temperature substantially different from that in which it was standardized with distilled water, corresponding corrections must be made.

The capillary tube can be made so that it takes distilled water anywhere from three to six or seven seconds to reach the mark; about five or six seconds is the most convenient and practical time, and a little practice will enable one to make the pipette of the proper size. If it takes too long, break off a little of the pipette, if not long enough a new one must be made.

The clinical observation is made as follows: One arm of the V-shaped tube, made of glass tubing with a lumen of 1 1/2 mm. is partially filled with blood by holding it against the under surface of a drop exuding from the side of the tip of the finger, as I prefer, or the lobe of the ear. Five or six drops of blood are required. This tube is then held by an assistant or in a suitable clamp by the arm through which the blood has been collected, leaving the clean arm of the tube for observation. The bulb and capillary tube are arranged precisely as above described for the experiment with distilled water and the end of the capillary tube passed down the clean arm of the V-shaped tube until it is close to the surface of the specimen of blood. Then with the stop-watch in the other hand it is quickly plunged into the blood and the stop-watch started at the same instant, the watch being stopped, as before, when the moving column reaches the mark at (5). It is then simply a matter of dividing the time required by the blood to pass through the capillary tube, by the time required by the distilled water, which in the pipette illustrated was five seconds. If with this pipette it would take twenty-five seconds for the blood to reach the mark the viscosity of the blood would be just five.

This observation can be made in less than three minutes, and is, in my opinion, sufficiently accurate to serve the purposes of clinical medicine.

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Sometimes the blood coagulates so rapidly that only a single observation can be made. This can be obviated by placing a crystal of hirudin in the V-shaped tube, as recommended by Bence and Determann. The blood will then remain fluid for twenty or thirty minutes. The greatest objection that I have found to the use of hirudin is that it is very hygroscopic and must be kept hermetically sealed or in a chamber with a desiccator. Its use, however, is quite unobjectionable, as it does not change the viscosity in the least or even modify rouleaux formation, so that it is available for other purposes in which slow coagulation is desirable as well as the determination of viscosity.

The capillary tube is cleaned in the usual way, first by washing with distilled water then with alcohol and finally with ether, and drying with a current of air. Should the tube be spoiled, as often happens, it only costs a fraction of a cent and a few minutes' time to make another.

The apparatus of Hess (Fig. 3) represents another attempt at simplification. I have neither seen nor used it, but believe that my own is simpler and more practical. With Hess's apparatus distilled water must be used at the same time with the blood (which complicates the procedure) and the two are drawn through their respective capillary tubes presumably by a negative pressure, the source of which is not shown in the illustration.

CLINICAL APPLICATION.

As already indicated, the viscosity of the blood under normal conditions undergoes considerable fluctuations owing to a variety of causes, among which may be mentioned the ingestion of a large quantity of water or food. Heavy muscular work has also been found to increase viscosity. Possibly by the increased transudation of fluid through the skin the same effect results as follows a sweating by electric light and other hot baths.

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These variations will be readily understood when the factors which influence viscosity are taken into account. Among these the percentage of blood corpuscles is perhaps the most important, which Heubner, as already stated, calculates is accountable for the greater part of its viscosity. It has been clearly shown, however, that there are constituents in the plasma which influence it very much. It is probably in some way connected with the fibrin, as it has been found that the viscosity and coagulability increase and diminish together within certain limits.

The inhalation of chloroform and ether has no effect on viscosity. Alcohol, on the contrary, immediately and greatly increases it. This has been found to be the case whether alcohol was introduced into the circulation intravenously or by injection either into the stomach or duodenum. This experimental fact is of considerable importance in the pathology of chronic alcoholism and may help to explain some of its phenomena. The immediate effect of hemorrhage is to greatly lower the viscosity of the blood. This effect is quite lasting, contrary to that of the intravenous infusion of normal saline solution which also lowers viscosity, the effect being very evanescent, however.

The diminished viscosity of the blood following venesection very probably has much to do with the well known therapeutic results in the way of relieving an embarrassed heart, etc., under certain pathologic conditions. There is no doubt whatever that it greatly lowers the resistance in the peripheral circulation, as well as the volume of the circulating fluid.

Asphyxia influences viscosity more promptly and more profoundly, perhaps, than any other known factor. This is true whether the asphyxia is local or general. In one experiment, for instance, Determann found that by placing a ligature around one arm for twenty minutes, with the production of marked local stasis, the viscosity of the blood drawn from a finger on that side was

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nearly twice as great as in blood from the other arm. It had increased from 4.63 to 8.83.

These are among the most important observations made along this line. Their influence in pathology is far reaching. They clearly show why the heart becomes embarrassed, and raises a doubt as to the exact importance of vaso-constriction under such conditions, although it is, of course, quite possible that this may occur also. The direct effect of CO_2 in increasing the viscosity has not only been experimentally demonstrated, but Bence has actually lowered it again by the inhalation of oxygen, an observation which is also of great importance.

The clinical application of these facts is probably not limited to the acute conditions of cardiac embarrassment in which life is endangered, and in which venesection and the inhalation of oxygen are clearly shown to be indicated, but probably extends to the subacute or chronic conditions of respiratory incapacity.

An interesting observation of Determann, confirmed by others, is that in vegetarians the viscosity was materially lower than in meat eaters. The average for vegetarians was 4.32 and for meat eaters 4.85. As might be expected, the viscosity of the blood is low in the anemias. In a fatal case of splenic anemia under my observation the viscosity was less than 3. The red corpuscles had dropped to about 200,000 before the patient died.

One of the important questions concerning viscosity is its relation to Bright's disease and especially to the cardiac hypertrophy found in these cases. The question is exceedingly complex and not nearly so easily solved as might at first sight appear. There seems to be little doubt that when the average case of Bright's disease presents itself for clinical observation to those who were studying the viscosity of the blood that the latter was nearly always normal or low, and this without very much reference to the blood pressure at the time. In

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my own experience the viscosity has usually been between three and four, but every case was more or less anemic. The observations of Bence were to the same effect.

Hirsch and Beck studied twenty-four cases which were divided into three groups as follows: The first group included acute and subacute parenchymatous cases in which the following viscosities occurred: 5.29, 2.75, 4.28, 3.81, 2.92. The second group, chronic parenchymatous nephritis, with secondary contractions, contained the following: 4.87, 4.24, 4.26, 4.79, 4.74, 3.05, 3.42, 2.52. The third group, chronic interstitial nephritis, with primary contractions, showed: 5.91, 4.70, 4.89, 9.21, 4.52. It is interesting to note that the lowest viscosity in the entire series, namely, the last case in the second group, with a viscosity of 2.42, had a blood pressure of 242 mm. In three of the twenty-four cases the viscosity was above the average normal standard adopted by Hirsch and Beck. It is distinctly stated that in neither of these three cases was there any marked hydremia.

Herein lies the explanation of the comparatively low viscosity found so constantly in Bright's disease, for we usually have, as was found in twenty-one out of twenty-four of these cases, a more or less marked anemia. This anemia means, of course, a reduction in the number of erythrocytes on which, as pointed out by Heubner,[7] the viscosity very largely depends.

Just what would be found in the pre-anemic stage of Bright's disease, if these cases could be observed at this time, is a question which is not yet settled, and in its very nature is almost impossible of solution. Few diseases are so insidious in their development, so completely masked in their early stages as this, and, as a rule, when first seen the blood has undergone serious changes and has become more or less hydremic. Ewart

7. Arch. f. exper. Path. u. Pharmakol., Leipz., liv, 149; Id., liii, 280.

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contends that the viscosity is high at this time and is one of the factors in the production of the cardiac hypertrophy. Hirsch and Beck, supported by Bence, controvert this view, and claim for reasons that do not appear to me entirely conclusive, that increased viscosity is not a factor in producing the cardiac hypertrophy. The difficulty lies in observing the cases early enough to determine the conditions during the early stages of the hypertrophy, which is usually well marked when the case is recognized.

As shown by Determann, Hirsch and Beck and Bence, those who eat considerable quantities of meat have a higher viscosity, and in at least one of the series of cases above quoted in which there was no anemia, the viscosity was extremely high. When the effect of a free meat diet is taken in connection with alcohol, together with the toxic conditions which we now believe to be antecedent to the fully developed picture of Bright's disease, high viscosity appears to be probable in the preliminary stages. Just in so far as it does exist must it be reckoned with as a factor, although very possibly a subordinate one, in increasing the work of the heart, the physiologic result of which is hypertrophy.

In the cases with arterial disease the high resistance in the peripheral circulation is much more important in increasing the work of the heart and with a very low viscosity may give us a high blood pressure, as in the case above quoted. It seems to me, therefore, that while the effect of the toxins on the heart muscle may reasonably be regarded as an excitant of over-action on the part of the heart and consequently of hypertrophy, as originally set forth by Bright, that it is strictly in accordance with clinical and scientific data to regard an increased peripheral resistance both from a diminished caliber of the blood vessels and an increased viscosity as important factors in the production of the cardiac hypertrophy of Bright's disease. Just how large a rôle in-

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creased viscosity plays and in what group of cases it is most conspicuous it is impossible at present to say.

Not very much can yet be said concerning the therapeutics of high viscosity. The iodids undoubtedly modify it in some way, and are therefore indicated in suitable cases in small doses. In cases of polycythemia the treatment is that of the blood condition. In several cases under my observation with viscosity sufficiently high to form important factors in circulatory disturbances this condition was present in a very marked degree. In one case with a red cell count of 7,250,000, the viscosity was very nearly seven. There was associated with the polycythmia, hyperchlorhydria and neurasthenic symptoms. During a month's treatment in the hospital, along with the general improvement, the red cell count gradually dropped to about 5,000,000 and the viscosity to 5.5.

The obscure modifications of the plasma which undoubtedly influence viscosity can only be treated in a general way by improved nutrition, elimination, etc., as their precise character is entirely unknown. The withdrawal of alcohol and a reduction or withdrawal of meat in the diet is clearly indicated in these cases. The importance of a free supply of oxygen is also clearly indicated by the experimental work with asphyxia and the inhalation of oxygen. Outdoor life, moderate exercise, the best of hygiene and everything that tends to uplift the physical condition of the patient should and usually will tend to lower excessively high viscosity and thus free the peripheral circulation.

A low viscosity usually means simple hydremia the therapeutic indications of which are plain enough, though not always effective.[8]

CONCLUSIONS.

1. The viscosity of the blood is an important physical property dependent on both the corpuscles and the

8. Lommel, F.: Deutsches Arch. f. klin. Med., Leipz., 1904.

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plasma which furnishes a considerable part of the peripheral resistance to the circulation of the blood.

2. It undergoes considerable fluctuations as a result of physiologic changes connected with food, drink, exercise, etc.

3. Under pathologic conditions, the changes are much greater and the viscosity may be so much increased, as, for instance, when the blood is charged with CO_2 that the heart will be embarrassed in overcoming it.

4. The viscosity of the blood is actually low in the large majority of cases of chronic Bright's disease owing to existing hydremia, but there is probably an earlier stage with high viscosity.

5. It seems probable that an increased peripheral resistance in the circulation of the blood due, in part, to increased viscosity, is at least one of the factors in the production of the cardiac hypertrophy of Bright's disease.

6. Venesection greatly lowers the viscosity of the blood by withdrawing its solids and attracting the fluids from the surrounding tissues.

7. Alcohol introduced into the circulation greatly increases viscosity, and in this way interferes with the peripheral circulation and burdens the heart.

8. The approximate determination of the viscosity of the blood as a routine clinical procedure is desirable in nutritional and toxic disorders, and should be made by a method rapid and simple enough to be practicable for routine use.

9. Individual diseases do not change viscosity in any characteristic way except as they incidentally modify the blood.

10. The determination of viscosity should be made promptly before the corpuscles have time to settle, for obvious reasons. The use of hirudin, if it leads to considerable delay, is therefore objectionable unless the homogeneous mixture of plasma and corpuscles is again reproduced.

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11. The viscosity of the blood is not altogether dependent on its specific gravity, for in fevers the former may be high and the latter very low.

DISCUSSION.

Dr. Henry B. Hemenway, Evanston, Ill.: I believe the subject of Dr. McCaskey's paper to be one of the most important ever brought before the attention of the general practitioner. Dr. McCaskey, however, has kept the heart especially in view, whereas I have been looking especially at the general circulation. For example, pure water would flow for a long time and uninterrupted through a pipe of a certain size. If the water is impure, however—as, for example, sewage from the kitchen sink—the greater viscosity would clog the pipe. So, with increased viscosity of the blood there would be an obstruction to the circulation through the capillaries, and this tends to produce a closure in the capillaries. An interesting point is that, before the absolute closure, the arterial pressure is much greater than the venous pressure and there is the tendency for the serum to get into the tissues. This exuded fluid then gains an entrance back into the circulation by absorption through the small veins and lymphatics. This results in a gradual straining out of the organized elements of the blood and, in such cases, one would find an increasing anemia. This increased viscosity of the blood, as well as sometimes an increased coagulability of the blood, is found in certain forms of Bright's disease and other conditions. Coagulability of the blood does not always accompany an increased viscosity of the blood. Yet there are times when the coagulability is accompanied by increased viscosity of the blood. If the coagulability and the viscosity of the blood are increased at the same time, there is an inclination toward the production of a thrombosis, a thrombosis occurring in any portion of the body. So in this there is one of the most common conditions concerned in the production of thrombotic apoplexy. In the production of an attack of this form of apoplexy there is an increased viscosity, a slowing of blood current, with an increased coagulability of the blood which tends to produce thrombosis.

Dr. Nathan Rosewater, Cleveland: The viscosity of the blood has interested me for a long time. Viscosity of the blood is reduced by the iodids; this does not require very large doses, only from five to ten grains. The method Dr. McCaskey used I believe to be a good one; but would it not be practical to drop the blood directly from the pipette through alcohol or ether, noting the time, dropping it through long column of the fluid?

Dr. J. F. Hultgen, Chicago: With regard to the relation between alcohol and the viscosity of the blood, Dr. McCaskey

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has omitted to give the dose administered, the kind of alcoholic beverage used, and as to whether there were any other morbid conditions coexisting at the time of alcohol ingestion. Moreover, he has not suggested how it does produce this increase in viscosity.

Dr. Louis Faugeres Bishop, New York: The difficulty with which the blood circulates has a distinct relation to the increased red-cell count. In my experience there is a large number of cases of circulatory troubles in which high tension exists, cases occurring in overnourished people suffering from high arterial tension; the red-blood count has been considerably above 5,000,000. I have learned to expect in a certain type of cases that the red-cell count would be above the normal. Again I could expect the condition to improve with a reduction in the red-cell count by suitable hygiene. This shows to me that the red-cell count has an important bearing in certain conditions.

Dr. G. W. McCaskey, Fort Wayne, Ind.: In regard to the point mentioned by Dr. Bishop, an estimation of the red-cell count is certainly important. I am glad to hear Dr. Bishop say that in some cases of polycythemia the red-cell count dropped with improved hygienic conditions, for this is in accord with my experience. I do not know how alcohol acts on the viscosity of the blood. Twenty minutes after its introduction into the duodenum of animals there occurs an increased viscosity. Just what the change is I do not know. The experimental dose is from 5 to 20 c.c. I believe that the iodid of potassium lowers the viscosity of the blood. In studies on the viscosity of the blood I believe that we have found a partial explanation of how the iodids act in chronic cardiovascular diseases. As the viscosity is lowered, peripheral resistance is diminished.

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PAROXYSMAL HEMOGLOBINURIA.*

ACCOUNT OF TWO CASES.

C. F. HOOVER, M.D. AND C. W. STONE, M.D.
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The first of the two patients, A, who furnish the basis of this report is a man 29 years old, who was born in Hungary, and served as a soldier in that country. During his military service he suffered much from chilblains during the winter, but he never had an attack of hemoglobinuria until December, 1902, eight months after coming to America.

During the summer of 1902 he lived in Saginaw, Mich., where he suffered much from mosquito bites.

There is absolutely no history of any infection or illness until December, 1902, when the patient first observed the attacks of hemoglobinuria, which were invariably associated with exposure to cold. We had no opportunity to observe any chilblains in this patient, but he says that when his feet or hands are thoroughly chilled they become very white, then blue and finally red, swollen and feverish. The swelling lasts several hours. According to the patient's account of himself, such an attack is always followed by a "black-water" attack.

Besides the chilblains there is nothing unusual in the history of paroxysmal hemoglobinuria of this patient. We found that attacks could be produced by exposure to cold. If the patient placed both hands in ice cold water for five minutes no hemoglobinuria followed. Sitting before an open window for fifteen minutes, clad in hospital garb, when the out-door temperature was about 10 degrees C., was followed by a characteristic chill, fever and hemoglobinuria. If one foot was placed in a pail of water, 8 degrees C., for thirty minutes an attack would follow. During the interim the patient's blood showed a coagulation time of three and one-half minutes. Directly after an attack, while the temperature was still elevated, the coagulation time was the same.

*This and the following article are reprinted in the Transactions from the *Archives of Internal Medicine*, in which they were first published.

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On March 3, 1908, the patient's blood-count was the following:

W. B. C., 7,800.	R. B. C., 4,520,000.
Hb. (Sahli), 92.	Tallquist, 85.

A differential count of 200 white cells gave the following results:

Polymorphonuclear cells,	158 =	79 per cent.
Small lymphocytes,	31 =	15.5 per cent.
Large lymphocytes,	8 =	4 per cent.
Eosinophiles,	3 =	1.5 per cent.

Repeated search for blood parasites proved negative, as did also all attempts to cultivate any organisms from the blood by the usual methods employed for such purposes. These examinations were made during the attacks and during the interims. On March 13 an attack was produced by placing the patient's foot in a pail of water at 8 degrees C. The following observations were made before, during and after the induced attack of hemoglobinuria.

The patient's foot was placed in the water at 10:50 a. m. Although there were some subjective premonitory signs of a chill at 11:50 it was not until 11:55 that the rigor was pronounced.

The temperature by mouth was:

At 10:20 a. m., 98.3 degrees.

At 11:20 a. m., 97.6 degrees. Subjective symptoms of muscular soreness.

At 11:50 a. m., 97.4 degrees. Chill apparent.

At 12:24 p. m., 100.2 degrees. Patient felt warm; urine passed rich in hemoglobin.

At 12:45 p. m., 102 degrees.

At 1:20 p. m., 100.2 degrees.

The arterial blood pressure was 146 mm. Hg., systolic pressure, before, during and after the attack.

The diastolic arterial pressure during the corresponding periods was 95. The chill and fever did not, therefore, modify the systolic or the diastolic blood pressure.

During the febrile period at 12:50 p. m. blood drawn into a syringe containing a small amount (2 per cent. of a 1 per cent. solution) of potassium oxalate and immediately centrifuged showed a distinctly pink serum which gave only the absorption bands of oxyhemoglobin to spectroscopic examination. Blood drawn and treated in the same manner before the patient's foot was placed in the cold bath revealed a normal serum. A few days later a cantharides plaster was applied to the arm.

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Three hours later when the serum was expected to accumulate in the underlying blister an attack of hemoglobinuria was induced. This serum was pink and showed the oxyhemoglobin bands under the spectroscope. A cantharides blister during an interim showed straw-colored serum.

The leucocyte count before an induced attack was 6,000; at the end of the chilly period the leucocyte count was 17,000 and was due to an increase of the polymorphonuclear cells. The leucocyte count made on March 7 was as follows:

At 9:00 a. m., before the chill,	= 6,000
At 11:30 a. m., after the chill,	= 17,000
At 1:00 p. m.,	= 15,000
At 4:00 p. m.,	= 11,000

During this attack the red cells were reduced 700,000 per c. mm. An ophthalmoscopic examination during one of the attacks revealed nothing abnormal in the eye-ground.

During the attacks the urine was colored a dark chocolate hue and showed nothing more than the presence of albumin, hemoglobin and casts of blood pigment.

From the above observations it was apparent that exposure to cold caused hemoglobinemia which was well pronounced before the febrile period. It is also clear that the rigor is associated with a slight lowering of the body temperature, and that the rise in temperature marks the cessation of the chill, which is unlike the relations between rigor, temperature and sense of warmth in the course of infectious diseases with which we are familiar.

The rise in temperature is associated with a pronounced polymorphonuclear leucocytosis.

The second patient B, an American, 25 years old, was admitted to Lakeside Hospital April 18, 1908. This patient was much more sensitive to cold than patient A. Without any history of illness or infection of any kind which could have any bearing on his present illness, B commenced having paroxysmal attacks of hemoglobinuria identical in character with those of A, eighteen months before admission to the hospital. As in A, the physical examination revealed absolutely nothing of an abnormal character. During warm weather he is perfectly comfortable, but if the thermometer is as low as 10 C., he is liable to an attack. He is particularly sensitive to a cold, moist wind, and has had as many as three attacks in one day. This patient gave no history of chilblains as did A, but at the conclusion of an attack there would be on the trunk and arms several small macules about one-sixteenth of an inch in

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diameter, in the middle of which a small blister would rise, from which the serum would escape during the febrile period and leave a very minute particle of desquamating epithelium apparent in the middle of the red areola. By the following morning all traces of the skin manifestations were gone.

The observations made on patient A were repeated on patient B. B suffered from a malady identical in character with that of A; the only essential difference being one of degree.

STUDY OF THE SERUM IN THESE CASES.

We then undertook a study of the serum of these patients from the standpoint of the side-chain theory, with the following results:

Although we were unable to find any organism in the patient's blood, either during the attacks or in the interims, it was clearly apparent that cold was essential for the hemolytic activation of the patient's blood.

Our first experiments consisted in attempting to activate the serum of these patients by exposing it to a low temperature, then warming the serum to 37 degrees C., and adding washed red-blood cells obtained from other patients with normal blood. After repeated trials with serum of these hemoglobinuric patients obtained by venous puncture and from blister serum (all of which were unsuccessful as long as the red cells were added to the serum when warm), we then chilled the serum after red cells had been added. When this precaution was taken, and the mixture warmed, hemolysis was complete within a very brief period.

All the experiments gave the same results with sera A and B.

Hemoglobinemic serum chilled in a salt and ice mixture at 5 degrees C., for thirty minutes, then put in an oven at 37 degrees C. for one hour, and after the serum again attained body temperature the red cells from a normal blood which had been repeatedly washed in physiologic salt solution were added to the serum and again put in the oven. The result was negative. The experiment and results are expressed in the following formula:

H. S. + 5° C. for 30 minutes + 37° for 1 hour + R. B. C. = 0.

In the next experiment the red cells were added before the mixture was exposed to a low temperature, and as soon as the mixture was again warmed complete hemolysis occurred. This was apparent by the disappearance of all cloudiness and the mixture becoming a clear ruby-red solution with a marked diminution of the viscosity of the serum.

H. S. + R. B. C. + 5° for 30 minutes + 37° C. for 10 minutes = +.

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The serum from patient B, with added red cells, was placed in the ice water for fifteen seconds, then put in a water bath heated to 56 degrees C. for ten seconds, at the end of which time hemolysis was complete.

The serum from patient A required a longer exposure to cold to produce hemolysis, which is quite consistent with the comparative clinical histories of the two men. B was much more sensitive to cold than A.

Accidentally we discovered that if the suspension of red cells in the serum of B was placed near a 32-candle-power incandescent electric lamp after having been exposed to cold, hemolysis occurred very promptly.

If a suspension of red cells in the serum was placed in a water bath at 15 degrees C. for five minutes and then exposed to the rays of the lamp, which registered 25 C. on a thermometer placed beside the test-tube, hemolysis was prompt and complete, that is, it occurred at the end of eight minutes.

A drop of the suspension of red cells in serum from B was placed under the microscope after the mixture had been exposed to cold. The rays of an Abbé condenser supplied sufficient heat to cause rapid hemolysis, which could be observed under the microscope. Many cells disintegrated by fragmentation and many faded from view as the hemoglobin content was dissolved out of the stroma. The entire field was then filled with fragments of red cells which would certainly have been mistaken for blood platelets so far as their morphology was concerned.

If the suspension of red cells in serum A or serum B were exposed to a low temperature for hours, no hemolysis occurred until the mixture was again warmed.

The reduction in temperature necessary in the laboratory tests to procure activation of this lytic serum gives a very striking suggestion of the radiation of heat from the surface of the body and the subsequent warming of the blood from the surface, as it again meets the visceral blood, and it also illustrates the maintenance of the internal heat by metabolism.

If serum from normal blood was substituted for the lytic serum, and washed red cells from either A or B were substituted for the normal red cells employed in the former experiments, hemolysis did not occur.

This showed that the lytic principle was contained in the serum, and that hemolysis did not result from a diminished resistance of the patient's red blood cells.

If to a suspension of washed red cells (5 per cent.) in 0.5 c.c. normal serum, 0.03 c.c. of serum B was added it was found to be the minimum proportion of lytic serum necessary to cause hemolysis. So it may be

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said that approximately 6 per cent. of serum B added to normal serum was required to cause hemolysis of 5 per cent. suspension of red cells.

Thus far it is evident that cold (15 degrees C.) is essential for fixation of the lytic principle to the red cells, and that a temperature of 25 C. is necessary for the accomplishment of hemolysis.

This behavior of the lytic principle strongly suggests the applicability of the side-chain theory to this instance of hemoglobinuria.

In an article by Donath and Landsteiner[1] we find they had the same experience as we had in producing hemolysis *in vitro* with the serum from a case of paroxysmal hemoglobinuria, and, although they attempted to prove the applicability of various steps in the side-chain theory, they failed to reactivate the serum after it had been inactivated by heat at 56 degrees C. for ten minutes.

If the serum is heated to 56 C. for twenty-five minutes all attempts to procure hemolysis by exposure to cold and then to 37 C. are futile. This shows, of course, that there is an unstable substance essential for hemolysis which answers to the complement of Ehrlich's theory. It now remains to be shown that there exists also a stable substance which serves as the amboceptor between the complement and the red cells. The first step to prove this point requires a successful reactivation of the serum. If done by the usual method employed in hemolytic experiments as tried by Donath and Landsteiner the result is negative.

0.5 c.c. of inactivated H. S. + washed R. B. C. + 5° C. for 30 minutes + 37° C. for one hour.

Now if the normal serum be added and the mixture is placed in the thermostat for many hours no hemolysis follows.

Inasmuch as a low temperature was required to procure fixation of the amboceptor to the red cell it seemed probable that reactivation experiments had hitherto failed because a low temperature was not employed in fixing the complementophilic end of the amboceptor to the haptophore of the complement. The following reactivation experiment proved successful.

0.5 c.c. of inactivated H. S. + washed R. B. C. + 0.25 c.c. of normal serum + 5° C. for 15 minutes.

The mixture was then warmed to 37 degrees C. and hemolysis followed immediately.

Thus it is apparent that cold is essential for the fixation of both the cytophilic and the complementophilic ends of the amboceptor.

1. Donath and Lundsteiner: München. med. Wchnschr.,

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The foregoing experiments prove the existence of two essential factors in the lytic principle of the serum, one of which is unstable and is rendered inactive by heat and is present in all human sera; the other factor is more resistant to heat and is present only in the serum of patients in whom exposure to low temperature produces hemoglobinemia.

Eason[2] in his experiments on the serum of a patient with paroxysmal hemoglobinuria by a different procedure showed practically the same point, although he failed to recognize the need of a low temperature to secure union between the complement and amboceptor. In his experiment red blood cells were added to the patient's inactivated serum and the mixture exposed to ice-water for half an hour. After the mixture was removed from the ice-water bath the complement from normal serum was added, how long after he does not state, but from our results the mixture must have been cold when the complement was added or hemolysis would not have occurred when the whole mixture was put in the brood oven.

If we are permitted to use the terms amboceptor and complement as applied to these two factors contained in the lytic serum it is incumbent on us to show that the union between the amboceptor and red cell is a biochemic union and one that can not be destroyed by washing the cells with physiologic salt solution after red cells have been exposed to cold in the presence of the inactivated serum from patients A and B respectively. At this period in our work we found that the oxalate serum did not differ from the serum which was procured by letting the serum separate out of the blood on standing. And as the serum could be procured more promptly and in larger amounts by centrifuging the oxalate blood, hereafter when the term H. S. is employed we shall mean hemoglobinemic serum to which 2 per cent. of 1 per cent. solution of potassium oxalate has been added.

The following is an experiment to show the fixation of the amboceptor which proved negative because the mixture was not exposed to a low temperature after the complement from a normal serum was added.

0.5 c.c. of inactivated H. S. + washed R. B. C. + 5° C.
for 1 hour.

The mixture was centrifuged and the supernatant fluid drawn off; the red cells were washed three times with large amounts of an isotonic salt solution. We then had presumably the red cells with the amboceptor fixed to them and clear of any of the excess of amboceptor which might have clung to the cells from the inactivated H. S.

2. Eason: Jour. Path and Bacteriol., 1906-7, xi, 169.

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If normal serum was now added to these (red cells + amboceptor), and the mixture placed in an oven at 37 degrees C. no hemolysis followed. In subsequent experiments, however, the mixture of (red cells + amboceptor) + normal serum was exposed to a temperature of 5 degrees C. for fifteen minutes and then hemolysis occurred as soon as the mixture was again warmed to 37 degrees C. Here again we have proof of the need of cold to procure fixation of the complementophilic end of the amboceptor to the haptophore of a normal serum.

The following experiments were made to show how the amboceptor could be exhausted from the lytic serum.

To 1 c.c. of inactivated H. S. five drops of a 10 per cent. suspension of washed red cells were added. The mixture was exposed to 5 degrees C. for one hour, then centrifuged and the supernatant serum drawn off. To the supernatant serum, red cells were again added and then 0.25 c.c. of normal serum added to the mixture. This mixture was exposed to cold for fifteen minutes and warmed to 37 degrees C. Hemolysis followed immediately, but it was not so pronounced as in our other reactivation experiments.

If to 1 c.c. of inactivated H. S. five drops of a 10 per cent. suspension of red cells were added, the mixture exposed to 5 degrees C. for one hour and then centrifuged, the supernatant serum again exposed to 5 degrees C. for one hour with five drops of a 10 per cent. suspension of red cells again added to the serum, and then centrifuged, the supernatant serum could not be reactivated.

Thus we have shown that if in two stages, ten drops of a 10 per cent. suspension of red cells be added to (1 c.c.) the serum and exposed to cold one hour each time, the amboceptor can be exhausted from the inactivated hemoglobinemic serum.

From a number of such experiments we learned that if the serum with red cells was exposed to cold less than one hour we could not procure fixation of the amboceptor.[3] Thus far we have shown that the hemoglobinemic serum contains two factors, one unstable and capable of being inactivated by exposure to a temperature of 56 degrees C. for twenty-five minutes and is a factor which is common to all human sera and answers to the complement of Ehrlich.

The other factor is found only in the hemoglobinemic sera and is resistant to 56 degrees C. for twenty-five minutes. This factor answers

3. Eason (Jour. Path. and Bacteriol., 1906-7, xi, 169) was able to procure fixation of the amboceptor after one-half hour exposure to cold. He was also able to exhaust the amboceptor by one-half hour exposure to cold.

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to the amboceptor of Ehrlich and can be fixed in a biochemic union to the red cells and can be exhausted from the hemoglobinemic sera if a sufficient number of red cells be suspended in the serum and the mixture exposed to a low temperature for one hour.

In watching hemolysis take place under the microscope and seeing the extreme rapidity with which hemolysis occurred in the test-tubes we were impressed with the striking similarity between this hemolysis and the hemolysis which occurs when small amounts of ether are added to a test-tube of isotonic salt solution with red cells in suspension.

The natural deduction from such observations was that the lytic principle of the serum attacked the lecithin, cholesterin or some other lipoid of the red-cell stroma. If this were the case, then an excess of a mixture of lecithin and cholesterin in the serum would satisfy the avidity of this lytic substance and protect the red cells from destruction.

The following experiment was made to show this point:

An emulsion of lecithin (Merck) in normal salt solution and a mixture of cholesterin (Merck) in normal salt solution were made. Both mixtures were very thick. Three drops of each were added to 0.5 c.c. of H. S. and the mixture permitted to stand for one hour. Washed erythrocytes were added to the mixture and the whole mass exposed to 5 degrees C. for thirty minutes and then put in the oven at 37 degrees C. for twelve hours. No hemolysis followed.

We found then in trying lecithin and chloresterin separately that lecithin did not in the least inhibit hemolysis, but that cholesterin always prevented hemolysis even in the slightest degree when present to the extent of 5 per cent. or more.

It remained to be shown how cholesterin exercised this inhibitory effect on hemolysis—whether cholesterin exercised merely a negative reactive influence or formed a union with the complement or with the amboceptor.

To the hemolytic serum an emulsion of cholesterin in normal salt solution was added, and the mixture permitted to stand in the oven at 37 degrees C. for one hour. The mixture was then centrifuged and the clear supernatant serum removed. To this clear serum cells were added and the suspension of cells in the serum put in the cold bath at 5 degrees C. for one hour. The mixture was then put in the oven at 37 degrees C. and at the end of twelve hours there was no hemolysis.

From this experiment we are permitted to assume there was a deflection of either the amboceptor or the complement. Unlike the behavior of the receptors of the red cells and the amboceptor, however, we found

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by repeated experiments that a low temperature was not favorable to anchorage of the cholesterin.

Cholesterin protected the red cells when 5 degrees C., 22 degrees C. and 37 degrees C. were employed, but the best protection seemed to be afforded when the cholesterin was in contact with the serum at 37 degrees C., so the affinity between the lytic principle of the serum and cholesterin was not identical in character with the linking of the amboceptor to the red cells.

The following experiments were then made to show whether the amboceptor or the complement was deflected:

One c.c. of the serum was inactivated by heating it at 56 degrees C. for twenty-five minutes. To this inactivated serum cholesterin in excess was added and the mixture permitted to stand at 37 degrees C. for one hour. The mixture was then centrifuged and the supernatant serum was clearer than the original unheated serum. We then assumed if cholesterin was fixed in this inactivated serum it must be fixed to the amboceptor.

To this clear serum washed erythrocytes were added and the suspension was exposed to 5 degrees C. for one hour. The mixture was then warmed to 37 degrees C. and 0.4 c.c. of normal serum was added and the mixture again chilled at 5 degrees C. for one hour. The mixture was then put in the oven at 37 degrees C. and in thirty minutes hemolysis was complete.

Therefore, treating the inactivated serum with cholesterin did not prevent anchorage of the amboceptor to the red cells.

The following method was then employed to show whether cholesterin deflected the complement or not in a reactivation experiment:

One c.c. of H. S. was heated at 56 degrees C. for twenty-five minutes. Red cells were then added and the mixture chilled at 5 degrees C. for on hour to fix the amboceptor. Cholesterin was then added to the mixture after it stood in the oven at 37 degrees C. for twenty minutes. Normal serum was then added to the mixture which was chilled at 5 degrees C. for thirty minutes. The mixture was then warmed and permitted to stand until the following day, but there was no hemolysis. This experiment shows that cholesterin acts by deflecting the complement.

Early in our experiments on these patients we tried calcium lactate as a remedy against hemolysis in both patients. They were given sixty grains a day over a period of two weeks, but at the end of that period the patients responded to cold as before and the hemolysis *in vitro* was unaffected. Nor did calcium lactate inhibit the hemolysis *in vitro*. After our experiences with cholesterin in the laboratory we administered

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cholesterin to these patients per os ten grains three times daily dissolved in olive oil. After ten days' trial of the cholesterin treatment we found that hemolysis *in vitro* was unaffected in both patients. The weather during this period was very warm, so neither patient had an attack, and although neither patient objected to repeated venous punctures for obtaining blood, they did not wish to expose themselves to an attack of hemoglobinuria by exposure to a cold foot bath. So whether the cholesterin therapy may offer protection against attacks due to exposure to cold or not remains undecided.

We make this statement in view of the experience which Widal and Rostain[4] had with their patients, on whom they were able to confer passive immunity by means of an antihemolytic serum. Although the patients of Widal and Rostain enjoyed immunity from attacks on exposure to cold, their sera was as actively hemolytic *in vitro* during this period of immunity as before.

We repeated the experiment of Widal and Rostain in procuring an antihemolytic serum from a rabbit by treating the animal with normal human serum.[5]

The rabbit was given four intraperitoneal injections during a period of three weeks. The amounts of normal serum used at each injection were 5 c.c., 15 c.c., 12 c.c. and 12 c.c. respectively.

To inhibit the lytic action of these patients' sera on red cells we found it necessary to employ about 12 per cent. of the inactivated immune rabbit's serum added to the serum of patients A and B. Normal human serum was hemolytic to the rabbit's washed red cells, but the sera from our patients was more strongly hemolytic than normal human serum.

In tube A was placed 10 c.c. of normal human serum and in tube B was placed 10 c.c. of hemoglobinemic serum from patient B. To each, i. e., A and B, were added 1 c.c. washed red cells from the rabbit. Both tubes were chilled at 5 degrees C. for twenty minutes and then both tubes were put in water (55 degrees C.) for fifteen seconds. Both tubes showed hemolysis immediately, but the hemolysis in tube B was more complete than in tube A. We also found that normal human serum completely laked the rabit's cells at 37 degrees C. in forty-five minutes without the previous exposure to cold.

The treated rabbit's serum also completely laked normal human red cells at 37 degrees C. in forty-five minutes without previous use of cold.

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4. Widal and Rostain: Compt. rend. Soc. de biol. de Paris, 1905, l, 321.

5. Eason (Jour. Path. and Bacteriol., 1906-7, xi, 203) employed the serum of a patient suffering from paroxysmal hemoglobinuria for the same purpose. Any human serum serves the same purpose.

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To test the antihemolytic property of this "sensitized" rabbit serum it was, of course, necessary to inactivate the serum at 56 degrees for twenty-five minutes.

We then found it was necessary to add as much as 12 per cent. of the inactivated rabbit's serum to the serum of patient B before hemolysis could be completely prevented. The antihemolytic property of our rabbit's serum was not so highly developed as in the rabbit of Widal and Rostain, probably because the rabbit was treated for a shorter time than was the rabbit in the hands of Widal and Rostain.

Widal and Rostain found that they could confer a passive immunity on their patients by subcutaneous injection of 25 c.c. of the inactivated serum from the sensitized rabbit. This immunity against cold lasted for only ten days. But during the immune period the lytic property of their patients' serum *in vitro* was undiminished.

This antihemolytic serum of the sensitized rabbit inhibits the hemolysis if it is added to the mixture of red cells and lytic serum after exposure to cold.

The protection from this serum is by virtue of deflection of the complement and is not due to antiamboceptor.

The question of etiology arises in relation to these experiments in hemolysis in the following manner:

1. Is the lytic property of these patients' sera due to a want of the normal antihemolysin which is presumed to be present in the sera of all normal animals?

2. Does the lytic principle of these sera partake of the character of a catalytic agent or a ferment?

3. Or is the lytic substance a biologic product of some form of infection which thus far has defied our attempts at detection?

If the first hypothesis were tenable we should expect to find hemolysis inhibited by the addition of inactivated normal human serum. This, however, is not the case. If inactivated normal serum is added to the fresh lytic serum in equal amounts and the mixture permitted to stand, either at a low temperature or at 37 degrees C. for an hour before red cells are added, hemolysis results after the mixture is exposed to cold just as in the original experiment.

The second hypothesis is not tenable because the amboceptor can be readily exhausted from the inactivated lytic serum by the exercise of its function of fixation to the red cells. A catalytic agent would not be sacrificed in such measured quantities by the exercise of hemolysis.

The third hypothesis does not admit of disposal. It is true that these patients are in good health as long as they are not exposed to cold, and

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the fact that they have hemoglobinemic fever can not be regarded as the direct effect of some organism. The abundance of cell shadows which must exist in the plasma of these patients after hemolysis occurs is quite sufficient to account for their fever. But patients may have infections without an elevation of temperature, and that, too, when organisms can be cultivated from their venous blood.

We had a patient in our wards at Lakeside Hospital during the past year who was a good example of an afebrile infection.

A young man 20 years old presented all the clinical signs of Hanot's type of hypertrophic biliary cirrhosis of the liver with splenic tumor and slight icterus. The patient remained three months in the ward and during that time a careful watch of his temperature never detected a rise above 99 degrees F. From the fluid gained by punctures of the spleen and the liver and from blood obtained from the vein of his arm we were able to cultivate a large motile bacillus with many characteristics of the common colon bacillus. It is true that the patient was ill, but he was not ill on accountof his infection, but on account of his diseased liver and spleen. With such experiences in mind it does not require a great flight of imagination to conceive of an infection of some kind being the underlying cause of our patients' hemoglobinemia.

Now, if such were the case we should expect to find some evidences of an antibody in the blood of the patient who has had his disease five years and who is less sensitive to cold than the other patient who has had his disease only one and a half years.

With this idea in view, inactivated serum from patient A was added in equal amounts to the fresh serum of patient B and inactivated serum from patient B was added to the fresh serum from patient A in equal amounts. These mixtures were permitted to stand one hour before red cells were added, but hemolysis resulted after the usual procedure of exposing the mixtures to 5 degrees C. and 37 degrees C. as in our earlier experiments.

As the matter at present stands we are justified only in saying that the hemoglobinemia which follows exposure to cold is due to some biologic product in the plasma which in its behavior admits of the demonstration of every step in hemolysis as expounded by the side-chain theory of Ehrlich.

In conclusion it gives us great pleasure to express our gratitude to Dr. J. J. Macleod, professor of physiology in Western Reserve Medical School, for valuable suggestions and consultations during the progress of our work.

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THE CLINICAL VALUE OF THE QUANTITATIVE ESTIMATION OF PEPSIN,

WITH SPECIAL REFERENCE TO THE METTE AND RICIN METHODS.*

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Beaumont's famous experiments showed that the gastric juice, even outside the body, had an active solvent action on food, and this led Müller to suspect the presence in it of a substance acting like diastase on starch flour. Eberle, in 1834, found this principle to be present in the acid gastric mucus. Müller and Schwann found that this was true of acid extracts of the mucous membrane, but that neither acid nor extract alone had any activity. Subsequent research showed that this was a property of the gastric mucus or secretion and not of mucus in general, as was originally surmised. Pepsin has since that time been exhaustively studied, and many remarkable facts have been demonstrated, the most interesting of which is Schütz's law, so-called, which is that the quantity of pepsin varies according to the square of the amount of albumin digested. In spite of all the effort that has been devoted to its study, pepsin, as such, has never been isolated in a pure state, so that it is impossible to estimate it quantitatively in a true sense of the word; all that can be done is to measure its effects and thus gain an idea of its concentration in a given solution.

The numerous quantitative methods for the estimation of the activity of pepsin have been so frequently reviewed that it is hardly necessary to discuss the older literature at length in the present paper. It will be sufficient to refer to the summaries in recent text-books, such as that of Boas, or to the articles of Koettlitz, Nirenstein and Schiff, Robin, Roth, and others. The following brief enumeration is, in part, after Roth:

1. The procedures of Bidder and Schmidt, Brücke, Gruenhagen, Jaworski, and Herzen are methods in which the stomach contents are

*From the Philadelphia Polyclinic and the Private Laboratory of Dr. John H. Musser.

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diluted until no further digestion occurs or in which a certain amount of albumin or fibrin is exposed to the digestive action of pepsin for varying periods of time. The amount of pepsin is calculated with reference to the dilution required or the time elapsed. Grützner and Bourget used fibrin colored with carmin and estimated the amount of pepsin by the intensity of the red color of the gastric juice produced by the solution of the fibrin. Spriggs utilized the change in the viscosity produced by digestion as a measure of the ferment action. These methods at the best can only give approximate results.

2. Klug (Van Valzah and Nisbet) used the biuret test as a measure of the albumin digestion. The elder Schütz, Oppler and J. Schütz also calculated the amount of pepton formed; Schütz by the polarimetric method and Oppler and J. Schütz by the estimation of the total nitrogen. Oppler used the Kjeldahl method, but surrounded his test with so many precautions to secure natural conditions of ferment action and accuracy in results that it is generally regarded as the best and at the same time the least available of all methods.

3. In recent years Mette, Hammerschlag, Bettman and Schröder, Solms, Gross and others have introduced methods which aim at the exactness of the last-named procedure, combined with ease of application. Solms' test is described in full below. Bettman and Schröder determined the amount of pepsin by observing the rapidity with which the foam produced by shaking up an albumin solution containing pepsin is dissolved. Some of those who have employed this plan do not appear to have been favorably impressed (Cobb). Hammerschlag's method is too widely known to require detailed description. It is based on an estimation of the albumin in a special solution, before and after digestion, by means of the Esbach albuminometer. We have used it in a few cases and have found, as far as our limited experience goes, that the results correspond in a general way with those obtained by the Mette method.

The following table illustrates a few comparative tests with the Mette and Hammerschlag tests:

No.	Mette.	H.
M 498	4.3 mm.	97 per cent.
M 638	3.9 mm.	87 per cent.
M 505	3.2 mm.	81 per cent.

Hammerschlag's test is generally regarded as inferior to that of Mette and possesses many faults which have been enumerated by Roth and others.

The method of Mette, as modified by Nirenstein and Schiff, is generally conceded to compare in exactness with that of Oppler. The technic which we have employed is not widely different from that of Nirenstein

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and Schiff (cf. Sahli) and was described by one of us, with Dr. Sailer, a year or two ago. For the convenience of those to whom it is unfamiliar it may be briefly described. Glass tubes, 1 to 2 mm. in caliber and 20 or 30 cm. in length, are filled by suction with white of egg, plugged with bread and boiled for five minutes. They are then sealed with sealing wax and after three days are ready for use. The test is carried out as follows: One c.c. of the gastric filtrate is diluted with 15 c.c. of N/20 hydrochloric acid. Two sections of tubing, 2 or 3 mm. in length, are added. A triangular file is sufficient for cutting the tubes. The specimen enclosed in a covered dish is kept in a thermostat at 37° C. for twenty-four hours. At the end of this period the column of albumin digested at each of the four exposed ends is carefully measured in tenths of a millimeter. An average of the four readings is recorded as the result, but it is usual to square this for comparison with other tests in accordance with Schütz's law.

The following examples will make this clear:

No.	Dil.	Reading.	Squares.	Relative Strength.
P.271	1 in 4	6.8	46	4
P.271	1 in 16	3.4	11.6	1
P.273	1 in 4	6.4	41	4 (approx.)
P.273	1 in 16	3.3	10.9	1

Mette's test thus modified excludes various errors which impair the value of many other methods, because it possesses the following advantages:

1. The acidity in all cases is rendered approximately uniform without any tedious titrations being required.

2. The dilution is sufficient to overcome inhibition due to albumoses (Sailer and Farr), etc., or antiferments.

3. A uniform surface is exposed to digestion at all times.

4. Numerous observations show that it complies with Schütz's law in dilutions sufficient to avoid inhibition and to prevent a digestion of more than 4 mm.

Objections to the method are:

1. Albumin from different eggs or albumin coagulated at different temperatures or heated for different periods of time varies considerably in digestibility.

2. Differences in the caliber of the tubes beyond certain limits affect the readings.

3. Wide variations in the temperature of the thermostat have the same effect.

4. There is a decided personal index in measuring the column of albumin.

These faults can be largely overcome by the following measures:

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1. An unvarying technic and the use, possibly, of artificial or dried egg albumin of uniform quality (Onuf).

2. The use of an artificial pepsin control. For this purpose a 1 or 2 per cent. solution of a standard pepsin should be employed, diluted 1 in 16 in the same way as the specimens to be examined.

3. A uniform method of measurement.

In these tests we employed an ordinary clinical microscope (low power) fitted with a movable stage and vernier scale.

Two illustrations will show the value of controls where there are wide discrepancies:

(a) No.	Mette.	(b) No.	Mette.
M 273	5.2	M 511	4.4
M 282	5.8	M 520	2.8
M 251	2.8	M 638	3.9
Control pepsin, 1/16 per cent.	4.2	Control pepsin, 1-16 per cent.	2.8

Comparison in these cases leads us to lay less stress on the high figures obtained in the first experiment. Similarly M. 251 can be regarded as a case of greatly diminished pepsin, while M. 520 with the same reading is merely a low normal.

Jacoby, in 1906, in a short article disputing Pawlow's assertion that pepsin and rennin were identical, introduced a new method of determining pepsin, which, he claims, decided definitely the individuality of the two ferments. This method was by means of ricin, a solution of which, he found, was cleared up by pepsin. Although this peculiar property had been observed by him some time before while pursuing his study of ricin, its adaptability to clinical use was not brought forward until Solms published his paper in 1907.

Jacoby had found that, if pepsin were added to a 1 per cent. solution of ricin in salt solution, the cloudiness due to the albuminous substances in the ricin disappeared rapidly and completely. Working on this under Jacoby's direction, Solms evolved the following simple procedure, the only fluids needed being a solution of ricin and a N/10 hydrochloric acid solution:

The ricin solution is made by dissolving 0.5 gram of ricin in 50 c.c. of a 5 per cent. sodium chlorid solution and filtering. (The recin used by Solms was obtained from the Vereinigte chemische Werke, Charlottenburg, Salzufer 16, costing 2 marks for 10 grams. Solms preferred this preparation of ricin to Merck's, principally on account of the limited supply and the great cost of the latter.) The filtered ricin solution has a somewhat cloudy appearance, but on the addition of 0.5 c.c. N/10 hydrochloric acid solution becomes decidedly milky. The milky appearance is cleared up by pepsin.

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His technic is as follows: The gastric juice is obtained by extracting the stomach contents one hour after the ingestion of an Ewald-Boas test breakfast. He tests this for the presence of free hydrochloric acid, then determines the total acidity, and in appropriate cases examines for lactic acid. According to his findings he makes varying dilutions of the contents with distilled water. In cases of hyperacidity he dilutes the filtered contents from 1:100 to 1:10000, whereas in cases of anacidity or subacidity the dilutions vary from 1:10 to 1:100. In normal cases he dilutes from 1:100 to 1:1000.

In each of the five test tubes he puts 2 c.c. of the filtered ricin solution; then with another graduated pipette he adds 0.5 c.c. N/10 hydrochloric acid, which causes the mixture to become very cloudy. Having numbered the test tubes 1, 2, 3, 4 and 5, he puts in the first tube 1 c.c. of boiled gastric juice; in the second, 0.9 c.c.; in the third, 0.8 c.c.; in the fourth, 0.5 c.c., and in the fifth, 0 c.c. Then he takes the unboiled juice and, having diluted 1 c.c. of juice with 99 c.c. of water, he puts in the first test tube 0 c.c.; in the second, 0.1 c.c.; in the third, 0.2 c.c.; in the fourth, 0.5 c.c., and in the fifth, 1 c.c., so that in each tube there are 3.5 c.c. of fluid. The test tubes are then corked and put in an incubator, where they are allowed to stand for three hours; at the end of this time they are taken out and the tubes examined to see with what dilution the ricin has been cleared up. If an incubator is not at hand the tubes can be left at room temperature, of course for a correspondingly longer time.

In order to obtain a convenient expression of the pepsin content of a gastric juice, he designates that amount of pepsin contained in 1 c.c. of a 1:100 dilution, which is capable of clearing up the ricin solution after three hours' standing in an incubator, as 100 pepsin units. This he has decided on as the normal standard, because after many examinations of specimens of normal acidity he found the ricin to be cleared up by 1 c.c. of a solution diluted 1:100. Solms considers the normal acidity to be 40 to 60, and anything above or below this to be hyperacidity or hypoacidity, and gives tables showing the pepsin content in these various conditions. His tables show no fixed relation between the acidity and the amount of pepsin, except in those cases in which the acidity is very low or the free hydrochloric acid entirely absent, under which conditions the pepsin will be found to be low also. Solms thinks that from a study of his tables he has learned nothing which would tend to show that the estimation of pepsin has a diagnostic or therapeutic value.

Witte studied this new method of Jacoby and Solms and recommends it strongly on acount of its simplicity and cheapness. The only modification he proposes is to add a dilution of 1:50, since in his experience

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there have been cases where a dilution of 1 : 100 did not quite dissolve the ricin. His conclusions are about the same as those of Solms, namely, that the normal pepsin unit is between 100 and 200 and that there is but slight relation between the acidity and the amount of pepsin, except in cases of lowered acidity, in which the pepsin is likely to be lower. Witte made a few comparisons with the Mette method, but prefers the ricin procedure.

TABLE 1.—NORMAL ACIDITY—40-60.

Serial No.	Total Acid.	Free Hcl.	Ricin.	Mette.	Diagnosis.	Case No.
1	40	0	100 not clear.	1.6 (2.6)	Carcinoma pylorus.*	F. S.
2	40	30	100-200	3.8 (14.4)	Hyperchlorhydria	M., 464
3	42	+	100	3.1 (9.6)	Chr. constipation	P., 335
4	43	+	Not made.	3.3 (10.9)	Hyperchlorhydria	P., 273
5	44	26	200	3.2 (10.2)	Gastro-enteroptosis	M., 505
6	48	10	100	4.9 (24)	Chloro-anemia	M., 311
7	50	18	10	3.9 (15.2)	Chr. gastritis	M., 570
8	50	30	200	4.4 (19.4)	Migraine—dilatation of stomach	M., 511
9	50	+	100 not clear.	0.5 (0.25)	Pyloric obstruction†	G. C.
10	50	+	Not made.	3.2 (10.2)	Constipation—nervous dyspepsia	P., 300
11	50	+	Not made.	4.9 (24.0)	Chr. constipation	F. B.
12	54	34	100-200	4.3 (18.5)	Gastric neurosis	M., 434
13	54	36	100	Not made.	Tubercular enteritis	M., 659
14	56	24	100	Not made.	Cholecystitis	M., 884
15	58	30	100 not clear.	3.7 (13.7)	Hyperchlorhydria	M., 402
16	58	34	100	3.0 (9.0)	Neurasthenia—gastric neurosis	M., 449
17	60	45	100	5.2 (27.0)	Cholecystitis—hyperchlorhydria	M., 791
18	60	+	100	5.0 (25.0)	Malnutrition—chr. pancreatitis(?)	S. C.
19	45	20	100	Not made.	Gastric neurosis	M., 663

* Without preliminary lavage. Lactic ac. +. Lower dilution of ricin not made.
† Probable carcinoma. Butyric acid. Lower dilution of ricin not made.

Gross advances a new method which he claims to be simpler than the foregoing. His method is based on the precipitation of undigested casein by sodium acetate, but we have had no opportunity of studying its value. Gross claims that the Jacoby-Solms method is open to criticism on one point, and that is that the ricin they used is very impure and that there is no way of determining just what foreign bodies are mixed with it. He also objects to the method on grounds of expense, but this, depending merely on a personal point of view, requires no comment.

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In making our studies we have followed closely the technic as laid down by Solms and have seen no reason to make any change or modification. The only drawback we have encountered is that the ricin solution must be freshly prepared. We tried making up a large amount, and filtering it only as needed, but the filtrate was so cloudy that it was difficult to determine the extent of pepsin digestion, as the solution did not become clear even when the gastric juice was but little diluted. After the ricin solution is once made, the preparation of the five tubes for peptic digestion occupies very little time, not more than seven minutes on an average, when once the technic has been perfected.

The results of our studies are shown in the accompanying tables, which are self-explanatory.

SUMMARY OF THE TABLE OF NORMAL ACIDITY (40-60).

Apart from three cases, Nos. 1, 9 and 18, the ricin and the Mette methods gave results within normal limits. In our table the ricin results of Case 1 is reported as "100 not clear," but in this case, as in Case 9, lower dilutions than 1:100 were not made. Finding that 100 was not digested, we should have begun with a dilution of 1:10, when there would doubtless have been a low reading corresponding with that by the Mette method. Case 18 shows the Mette result to be at the extreme upper limit of the normal, while the ricin remains exactly normal. From a study of the table we see that, apart from those cases with organic acids or diminished free hydrochloric acid, no aid in diagnosis other than that derived from the ordinary chemical examination has been obtained by the determination of pepsin. In Case 9 retention, favoring the production of organic acids, is the cause of the relatively high acidity. The same case (Table 2, 10), after lavage, showed a very low acidity and a minimal amount of pepsin. Therapeutically, the table is suggestive, but nothing more.

SUMMARY OF THE TABLE OF LOW ACIDITY (BELOW 40).

With low acidity the pepsin is also low, both by the ricin and Mette methods. In two instances, Cases 8 and 5, the Mette was normal, while the ricin was absent or diminished, respectively. This discrepancy can be explained, as the controls for the Mette tests were also high. In Case 14 the ricin was normal, while the Mette was subnormal. We have no explanation to offer for this variation.

Pepsin determination seems to be of value in distinguishing simple gastritis and neuroses from achylia and carcinoma. In the last two the

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pepsin is invariably very much diminished, whereas in the first two it is unaffected or but slightly altered. In this we disagree with Witte, who found that pepsin was always low in neuroses.

SUMMARY OF THE TABLE OF HYPERACIDITY (ABOVE 60).

With very few exceptions, the ricin and the Mette methods coincided in cases of hyperacidity, although the former is not capable of showing the finer gradations of the latter. In two cases, 27 and 55,

TABLE 2.—SUBNORMAL ACIDITY—BELOW 40.

Serial No.	Total Acid.	Free Hcl.	Ricin.	Mette.	Diagnosis.	Case No.
1	35	0	10-20	2.3 (5.3)	Endarteritis—chr. tuberculosis. . .	M., 140.
2	34	+	Not made.	3.4 (11.6)	Constipation—Subacidity.	P., 271.
3	28	6	10	2.8 (7.8)	Cholelithiasis—gastritis	M., 251.
4	26	0	20-50	2.0 (4.0)	Polycythemia—chr. gastritis*. . . .	M., 314.
5	26	8	10-20	3.3 (10.9)	Gastric neurosis	M., 579.
6	25	0	10	0.8 (0.64)	Pyelitis	M., 189.
7	22	0	10	1.0 (1.0)	Chr. gastroenteritis†.	M., 313.
8	22	0	0	3.4 (11.6)	Chr. gastritis	M., 571.
9	20	0	0	0.1 (0.1)	Anacidity	M., 576.
10	12	0	Not made.	0.5 (0.25)	Carcinoma pylorus‡	F. S.
11	12	0	Not made.	0.8 (0.64)	Chr. Diarrhea—achylia gastrica§. .	P., 350.
12	12	0	Not made.	0.5 (0.25)	Incipient tbc.—splanchnoptosis achylia gastrica	P., 15.
13	4	0	Not made.	0	Achylia gastrica‖	P., 270.
14	18 (1)	+	100-200	2.4 (5.7)	Spastic stricture of esophagus. . . .	P., 302
15	34 (2)	+	100 not clear.	2.2 (4.8)	ib**	ib.
16	6 (3)	0	10 not clear.	0	ib††	ib.

* Vomitus.
† Lactic acid present.
‡ Lactic acid present after lavage. See F. S., Table 1.
§ No lactic acid.
‖ Lactic acid present.
** Lower dilution of ricin not made.
†† Contents of esophageal dilatation.

the ricin was 1,000, while the Mette was also high. In Case 37 there was a disproportion between the two methods, the ricin being 1,000 while the Mette showed a normal value. In this case two dilutions of ricin were made, one of 1:100 and the other 1:1000, in each of which the result was 1,000 units. In two other cases, 53 and 56, the ricin was abnormally high and the Mette low, which can be explained by the low result obtained in the control experiment.

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Here our efforts to find some diagnostic aid in the quantitative estimation of pepsin have met with failure. The fact that there is no definite relation between the degree of acidity and the amount of pepsin might suggest the use of artificial pepsin in occasional cases.

COMPLETE SUMMARY.

Our tests indicate that the normal variation of the Mette method is between 3 (9) and 5 (25), of the ricin method 100 to 200. In carcinoma ventriculi, achylia and occasionally in chronic gastritis, the pepsin determination reveals values below the minimal normal, but as a rule in neuroses and chronic gastritis the pepsin is relatively but little affected in contradistinction to carcinoma and achylia, and this would seem to be of assistance in making a differential diagnosis between these conditions. We have found, as have others, that within normal limits there are wide variations without apparent relation to the acidity, but at present we are not in a position to draw any diagnostic or therapeutic conclusions from these observations.

The results obtained with the ricin method correspond with those shown by the Mette method; that is, normal values and subnormal values are clearly shown, but the finer variations are not seen and when present frequently do not correspond with the Mette results. This is true even when we have made allowance for differences in the Mette tubes by means of the controls referred to above.

Both tests are valuable as rough quantitative methods, and they are carried out with equal facility. The Mette has the advantage of excluding variations due to differences in acidity without requiring any previous titration. There has been no attempt made to see whether the ricin method follows the law of Schütz, nor has there been any attempt made to bring the various tubes to a uniform acidity. The variation in the acidity of the five tubes would seem *a priori* to be fruitful of grave errors. This could probably be obviated by suitable dilutions with N/20 hydrochloric acid, similar to those employed by Nirenstein and Schiff in their modification of the Mette method. These questions may form the basis of a supplementary communication.

We have made little therapeutic use of the knowledge we have obtained. The wide variations in the pepsin values would suggest that the drug has been too much despised by stomach specialists, though this can not be said of practitioners in general. It would seem to be indicated in cases showing subnormal peptic values, with preservation of at least a fair degree of acidity. In chronic gastritis with low acidity and low pepsin, in achylia and in carcinoma it would be necessary to add hydro-

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TABLE 3.—HYPERACIDITY—ABOVE 60.

Serial No.	Total Acid.	Free Hcl.	Ricin.	Mette.	Diagnosis.	Case No.
1	62	+	Not made.	3.2 (10.2)	Gastric ulcer	P., 310
2	62	+	Not made.	3.8 (14.0)	Constipation—chronic gastritis	P., 229
3	62	+	100	4.6 (21.2)	Cholelithiasis—pyloric adhesions	P., 289
4	62	30	100-200	Not made.	Goiter—dilated stomach	M., 871
5	62	34	100	2.8 (7.8)	Psoriasis—eczema	M., 520
6	62	36	100-200	4.1 (16.8)	Gastric neurosis	M., 300
7	62	16	10	3.8 (14.4)	Carcinoma pylorus*	M., 227
8	64	40	100	3.3 (10.9)	Neurosis	M., 575
9	64	30	100	Not made.	Nephritis—gastritis	M., 824
10	64	48	100	3.1 (9.6)	Adhesions(?)—hyperchlorhydria	M., 615
11	64	+	Not made.	2.3 (5.3)	Chronic gastro-enteritis	P., 272
12	65	40	100-200	3.6 (13.0)	Glycosuria	M., 500
13	65	40	100	3.4 (11.6)	Syphilis—neurasthenia	M., 176
14	66	40	100	2.8 (7.8)	Myalgia	M., 680
15	66	36	100	3.2 (10.2)	Tachycardia	M., 236
16	66	40	100	Not made.	Gastroptosis—gastric neurosis	M., 225
17	67	+	Not made.	3.4 (11.6)	Epilepsy	P., 324
18	68	24	200	3.6 (13.0)	Frontal sinusitis—neurosis—hyperacid.	M., 423
19	68	42	200	4.3 (18.5)	Gout—neurosis—alcoholic gastritis.†	M., 498
20	68	34	100 not clear.	3.3 (10.9)	Pancreatitis—hyperchlorhydria	M., 356
21	68	46	100-200	4.6 (21.2)	Cholecystitis—gastric ulcer	M., 322
22	68	+	100	4.0 (16.0)	Hypochondriasis	F. W.
23	68	+	Not made.	3.2 (10.2)	Gastric ulcer	F. M.
24	68	44	100-200	5.9 (34.8)	Chr. appendicitis—gastric neurosis	M., 757
25	70	40	100	Not made.	Jaundice—cholecystitis	M., 664
26	70	40	100-200	4.0 (16.0)	Gastritis—hyperchlorhydria	M., 734
27	70	54	1000	5.8 (33.6)	Hour-glass contraction of stomach—pyloric adhesions.	M., 282
28	70	46	100	3.2 (10.2)	Fibroid of uterus—hyperchlorhydria	M., 371
29	73	+	Not made.	4.4 (19.4)	Constipation—hyperchlorhydria	P., 258
30	74	44	100	4.7 (22.0)	Hyperchlorhydria—pylorospasm—cholecytitis—chr. appendicitis.	M., 335
31	75	55	100	3.0 (9.0)	Hyperchlorhydria	M., 538
32	75	40	100-200	3.0 (9.0)	Exophthalmic goiter	M., 455
23	76	30	100	4.0 (16.0)	Appendicitis	M., 326
34	76	+	Not made.	3.0 (9.0)	Splanchnoptosis	S P.
35	76	+	Not made.	5.4 (29.1)	Gastroptosis—hyperchlorhydria	P., 193

* Vomitus.

† Hammerschlag, 97%.

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TABLE 3.—CONTINUED.

Serial No.	Total Acid.	Free Hcl.	Ricin.	Mette.	Diagnosis.	Case No.
36	78	56	100	3.5 (12.3)	Chr. appendicitis	M., 593
37	78	64	1000	3.8 (14.4)	Appendicitis—hyperchlorhydria.‡	M., 476
38	78	36	100	3.9 (15.2)	Hyperchlorhydria	M., 450
39	78	40	100	3.8 (14.4)	Gastric ulcer	M., 430
40	80	+	Not made.	4.0 (16.0)	Splanchnoptosis—incipient tbc	P., 296
41	80	55	100	3.4 (11.6)	Hyperchlorhydria	M., 678
42	80	55	100	3 0 (9.0)	Hyperchlorhydria	M., 585
43	82	52	100	3.0 (9.0)	Hyperchlorhydria	T. T. M.
44	82	52	100	3.8 (14.4)	Bronchitis—gastritis	M. 599
45	82	+	100	4.6 (21.2)	Cholelithiasis—hyperchlorhydria	F. B.
46	82	54	100	3.4 (11.6)	Gastritis	M., 689
47	84	52	100	3.1 (9.6)	Hyperchlorhydria	T. M. B.
48	84	60	100	Not made.	Neurosis—hyperchlorhydria	M., 883
49	85	35	100	2.9 (8.4)	Neurasthenia—gastroptosis	M., 692
50	85	55	100	2.6 (6.8)	Gastric neurosis	M., 667
51	86	48	100	4.9 (24.0)	Gastric neurosis	M., 561
52	86	58	100	5.2 (27.0)	Appendicitis—hyperchlorhydria	M., 273
53	88	54	500	2.8 (7.8)	Cholecystitis—hyperchlorhydria.§	M., 171
54	88	58	100-200	4.9 (24.0)	Frontal and ethmoidal sinusitis—hyperacidity.	M., 785
55	88	62	1000	5.3 (28.0)	Gastritis—hyperchlorhydria°	M., 334
56	95	60	500	3.1 (9.6)	Neurosis—hyperchlorhydria	M., 489
57	100	45	100	2.9 (8.4)	Gastric ulcer	M., 597
58	106	94	100-200	Not made.	Cystitis—enteritis	M., 828
59	110	62	200	3.7 (13.7)	Epilepsy(?)	M., 713
60	112	+	Not made.	4.2 (17.6)	Hyperchlorhydria	P., 341

‡ Two controls, first with dil. of 1:100; second with dil. of 1:1000.
§ Mette control also low.

chloric acid. In many cases it is doubtful if enough acid could be introduced, except occasionally with a stomach tube, to allow of normal proteolysis. A practical expedient (Sailer) is to saturate meat or milk, before taking, with dilute hydrochloric acid until free acid can be detected, after which a small dose of hydrochloric acid will suffice. Pepsin should be given in sufficient amounts to make a 1/4 to 1/16 per cent. solution in the contents of the stomach (estimated in advance). It should be given with or followed by at least twenty minims of dilute hydrochloric acid. Both may be repeated once or twice at short intervals to make up

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for the amount expelled into the duodenum. Gasterine, or the normal gastric secretion of the dog obtained through a Pawlow fistula, has been advocated by Frémont and others (see Bettmann) in doses of 100 to 500 c.c. We have had no experience with it, but it would seem to have no advantage over a mixture of pepsin and hydrochloric acid unless it possesses some "vital" or other property independent of its principal constituents.

In conclusion, we desire to acknowledge our indebtness to Drs. Musser, Sailer and Talley for the use of their clinical material, which we have freely used to supplement our own.

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DISCUSSION.

Dr. John H. Musser, Philadelphia: I can testify to the soundness of the observations that were made by Drs. Farr and Goodman.

Dr. M. J. Lichty, Cleveland: Does not the quantity of pepsin vary directly in a great measure with the quantity of hydrochloric acid? I feel that some of the best authorities have so regarded it, and therefore I wonder whether it was essential that such a careful determination of the quantity of pepsin should be made in chemical work under such circumstances. I am convinced that the longer one would watch these cases, and the more carefully one took note of the acid secretion of the stomach the more likely was one to get along without the use of pepsin in the digestion of foods.

Dr. J. R. Williams, Rochester, N. Y.: One question of importance is the value or the lack of value of most of the pepsin preparations on the market. I have examined most of these preparations by the method described, and the best of them, compared to the normal gastric juice, were of slight value; the real fact is that the normal gastric juice will digest more albumin in a few hours, from four to ten, for instance, than any of the so-called digestants would in two days, in the doses ordinarily recommended. I have had some experience in this, and on the point raised by Dr. Lichty on the work that was done in Kalamazoo. It has been proved that the presence of pepsin as a rule varies with the hydrochloric secretion; but in the cases of pronounced mental depression very often there is a very marked increase of hydrochloric acid and a total absence of pepsin.

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Dr. Nathan Rosewater, Cleveland: In regard to the protolytic value of pepsins on the market, my experience differs from that stated in this paper. I have examined pepsin in years gone by on a number of occasions and found those examined to be as represented, one grain being capable of digesting fully 3,000 grains of coagulated egg albumin—almost half a pound—practically as much as is eaten at a meal. Pepsin can do no harm, and often must prove beneficial. It is not without value even when there is no absence of gastric secretion. I believe that the proper administration of pepsin, hydrochloric acid, etc., to hasten the digestion of meals, especially in cases of neurasthenia and myasthenia when digestion is delayed, is of great clinical value, resting the tired glands, muscles and nervous apparatus involved. The saving of an hour's work, more or less, for each meal, must prove of great advantage. Regarding the test described, I suggest that the tube should not rest on the bottom as described, because the saturated solution as formed, being heavier than the solvent, soon surrounds the tube at the bottom of the vessel, preventing access of unsaturated solvent to the surface of the substance in the tube, and thus tends to vitiate the accuracy of the result of the tests; I therefore suggest that the tube be suspended near the upper surface of the solvent, so that, as fast as the substance in the tube enters into solution with the solvent, the saturated solution so formed at the surface of the solid, can sink toward the bottom, while successive portions of solvent can come in contact and dissolve fresh surfaces of substance in the tube; thus would be secured a continuously fresh surface and solvent, and a proper circulation of the solution formed which should tend to secure more uniformity and accuracy of result.

Dr. Edward H. Goodman, Philadelphia: Regarding Dr. Lichty's remarks about the quantitative and qualitative estimation of pepsin varying with the degree of acidity in Dr. Farr's and my studies of hyperacidity and normal acidity, there were no variations; but with the subnormal acidities the pepsin dropped with the hydrochloric acid. Dr. Farr and I have not been able to confirm the presence of hydrochloric acid and total absence of pepsin in nervous diseases. Dr. Rosewater's suggestion that the tube be suspended is one well worth taking up.

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PROCEEDINGS OF THE SESSION

TUESDAY, JUNE 2—AFTERNOON.

The Section was called to order at 2 p. m. in Sinai Temple by the Chairman, Dr. C. F. Hoover, Cleveland.

The Chairman read his address, entitled "Paroxysmal Hemoglobinuria."

Dr. Frank A. Jones, Memphis, read a paper on "Clinical Manifestations in Cardiovascular Disease."

Dr. James B. McElroy, Memphis, read a paper on "Cardiac Aneurism, with Report of a Case Associated with Mediastinopericarditis." Discussed by Drs. Robert Preble, Chicago; James B. Herrick, Chicago; William J. Butler, Chicago; and James B. McElroy, Memphis.

Dr. Frank Smithies, Ann Arbor, read a paper on "Clinical Aspects of Certain Mediastinal Tumors." Discussed by Drs. Thomas D. Coleman, Augusta, Ga.; Alexander Lambert, New York; Robert H. Babcock, Chicago; John Francis Herrick, Ottumwa, Iowa; and Frank Smithies, Ann Arbor.

Dr. A. W. Hewlett, San Francisco, read a paper on "Clinical Observations on Absolutely Irregular Hearts." Discussed by Drs. Robert H. Babcock, Chicago; Arthur D. Hirschfelder, Baltimore; W. S. Thayer, Baltimore; Edward F. Wells, Chicago; R. C. Allen, St. Joseph, Mich.; G. W. McCaskey, Fort Wayne, Ind.; and A. W. Hewlett, San Francisco.

Dr. John A. Witherspoon, Nashville, read a paper on "Malignant Septic Endocarditis." Discussed by Drs. Frank Billings, Chicago; O. M. Gilbert, Boulder, Colo.; Frank A. Jones, Memphis, Tenn.; M. Howard Fussell, Philadelphia; Frank Smithies, Ann Arbor; and John A. Witherspoon, Nashville, Tenn.

WEDNESDAY, JUNE 3—MORNING.

Dr. L. F. Bishop, New York, read a paper on "High Arterial Tension of Nervous Origin, with Diagnosis, Consequences and Treatment."

Dr. Joseph Eichberg, Cincinnati, read a paper entitled, "The Factors in the Estimation of Blood Pressure, with a Special Reference to the Tonometer of von Recklinghausen."

These two papers were discussed by Drs. W. Forest Dutton, Pittsburg; N. S. Davis, Chicago; Arthur D. Hirschfelder, Baltimore; I. J. Wolf, Kansas City; Joseph L. Miller, Chicago; S. St. John Wright, Akron, Ohio; C. F. Hoover, Cleveland; L. F. Bishop, New York; and Joseph Eichberg, Cincinnati.

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The Chairman appointed a Nominating Committee as follows: Drs. H. W. Hewlett, San Francisco; Alfred Stengel, Philadelphia, and Frank A. Jones, Memphis, Tenn.

Dr. H. D. Arnold, Boston, read a paper entitled, "The Physics of Physical Signs, with Special Reference to the Respiratory Murmur." Discussel by Drs. George N. Jack, Buffalo; Henry Sewall, Denver; Walter E. Scott, Adel, Iowa; T. C. Edwards, Salina, Cal.; and H. D. Arnold, Boston.

Dr. Clifford B. Farr and Dr. Edward H. Goodman, Philadelphia, presented a paper entitled, "Clinical Value of the Quantitative Estimation of Pepsin, with Special Reference to the Mette and Ricin Method." Discussed by Drs. John H. Musser, Philadelphia; M. J. Lichty, Cleveland; Williams, New York; Nathan Rosewater, Cleveland; and Edward H. Goodman, Philadelphia.

Dr. Arthur D. Hirschfelder, Baltimore, read a paper on "The Importance of Recent Studies on the Circulation for the Practice of Medicine." Discussed by Drs. W. S. Thayer, Baltimore; G. W. McCaskey, Fort Wayne, Ind., and A. D. Hirschfelder, Philadelphia.

Dr. G. W. McCaskey, Fort Wayne, Ind., read a paper entitled, "The Viscosity of the Blood and Its Clinical Significance." Discussed by Drs. S. P. Black, Pasadena, Cal:; Henry B. Hemenway, Evanston, Ill.; Henry French Goodman, Chicago; Nathan Rosewater, Cleveland; F. J. Hultgen, Chicago; L. F. Bishop, New York; and G. W. McCaskey, Fort Wayne, Ind.

WEDNESDAY, JUNE 3—AFTERNOON.

The meeting was called to order at 2 p. m. by the Chairman. A joint meeting, a symposium on typhoid fever, was held with the Section on Pathology and Physiology.

A paper on "The Channels of Infection and the Suppression of Typhoid Fever," was read by Dr. M. J. Rosenau, Washington, D. C.

Dr. Francis W. Peabody, Boston, read a paper on "The Value of Blood Cultures."

A paper on "Typhoid Bacillus Carriers," was read by Dr. William H. Park, New York.

Dr. David L. Edsall, Philadelphia, presented a paper on "Conditions Simulating Perforation in Typhoid Fever."

A paper on "The Metabolism of Typhoid Fever," was read by Dr. P. A. Shaffer, New York.

Dr. Thomas McCrae, Baltimore, read a paper entitled, "Treatment of Typhoid Fever."

These five papers were discussed by Drs. James M. Anders, Philadelphia; Lipston; Alexander Lambert, New York; M. J. Rosenau, Washington, D. C.; R. L. Jones, Nashville, Tenn.; Francis W. Peabody, Boston; Henry Albert, Iowa City, Iowa: Marks; William Litterer, Nashville, Tenn.; John A. Lichty,

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Pittsburg; D. L. Edsall, Philadelphia; Lawrence Litchfield, Pittsburg; H. B. Weaver, Asheville, N. C.; E. P. Joslin, Boston; W. S. Thayer, Baltimore; Henry B. Favill, Chicago; J. A. Witherspoon, Nashville; G. E. Munson, Springfield, Ill.; Lyon; Jackson; Baron; Bryan; Coffin; and Thomas McCrae, Baltimore.

THURSDAY, JUNE 4—MORNING.

The meeting was called to order by the Chairman, Dr. C. F. Hoover, at 9:30 a. m.

The Nominating Committee made the following report: Chairman, Dr. Joseph L. Miller, Chicago; secretary, Dr. Wilder Tileston, Boston; Orator on Medicine, James B. McElroy, Memphis; delegate, Dr. George Dock, Ann Arbor; alternate delegate, Dr. W. S. Thayer, Baltimore.

On motion of Dr. W. S. Thayer, Baltimore, the Secretary was empowered to cast one ballot for the election of the officers nominated.

Dr. Nathan Rosewater, Cleveland, read a paper entitled, "Disguised Starvation."

The Chairman said that it had been suggested by several men that a modification of the program of the meeting of the Section would add very much to the interest of the Section, facilitate discussion and increase the number of men who could serve on the program. He said that he would be glad to hear any motion or suggestion regarding the method of procedure by which this could be brought before the Section.

Dr Edward F. Wells, Chicago, said that it was clear that a section as large as the Section on Practice of Medicine of the American Medical Association, with a program containing forty papers, did not represent the proportion it should; that if it did represent the proper proportion, according to the present arrangements, it would be a physical impossibility to have them all read in the time allotted. It seemed to him that a further extension and presentation of papers might be made. He merely suggested that a certain number of selected papers be read as at present; that a certain number be printed in full, but with good abstracts, to be followed by an oral discussion of five or ten minutes' duration. These abstracts should be printed and presented to the members of the Section in advance of the session. Another division of the papers might be printed in full with discussion. Such papers might be full of details, of experiments, of observations, etc. He suggested that the number of papers be limited to eighty or one hundred, and that one-third be placed in one class, one-third in another and one-third in another.

He moved that the Chairman appoint a committee to consider this question and to report on it at the next session. He suggested also that this committee consist of ex-chairmen and ex-secretaries of the Section. This question was so broad and

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intricate, requiring the consideration of so many points, that he suggested that the committee report at the next session.

The Chairman said that the committee, as he understood, could report at its convenience.

The Secretary said that the Section officers had realized for some time that there should be a change made in the program. A number of men throughout the country were doing excellent work in medicine, and it had been impossible to accept desirable papers from them. Dr. Miller said that each year the Section officers had had applications from one hundred men, asking to present papers before the Section, and the majority of these papers had to be excluded because of the limitation of forty papers to each meeting. If they allowed twenty minutes for the presentation of each paper, and a proper amount of time for each paper to be discussed, it would be too much for the program.

The Secretary said that all this meant that there should be a change made in the program allowing of six, eight or ten-minute papers; this would allow more good men on the program. He thought that it would be a good idea if some arrangement could be made by which a paper could be presented in abstract form; then a number of men could discuss it, and still a larger number of papers be presented. An increase in the number of papers was a thing to be desired.

Dr. William S. Thayer, Baltimore, said that he would like to point out that if this method were adopted it would be necessary to know before the time of session what men would attend the session of the Association, and of their adherence to this Section. Those desiring to attend should notify the authorities; then the abstracts of papers could be sent them prior to the session. Dr. Thayer said that this was what was done in the international congresses.

Dr. Wells' motion was carried.

The Chairman appointed the following men to serve on this committee: Drs. George Dock, Ann Arbor; Alexander Lambert, New York; Allen A. Jones, Buffalo; Edward F. Wells, Chicago.

Dr Henry Buswell, Buffalo, read a paper on "A Case of Syphilitic Infection of Fourteen Years' Duration with Protracted and Unusual Febrile Symptoms." Discussed by Drs. Joseph L. Miller, Chicago; William J. Butler, Chicago; Charles G. Stockton, Buffalo; William S. Thayer, Baltimore; C. F. Hoover, Cleveland, and Henry Buswell.

Dr. Walter Bierring, Iowa City, read a paper entitled, "Remissions in Pernicious Anemia and Their Significance." Discussed by Drs. Charles G. Stockton, Buffalo; William S. Thayer, Baltimore; Alfred Stengel, Philadelphia; Adolph Th. Paulson, Chicago; W. M. McCabe, Nashville; Hugo A. Freund, Detroit; J. A. Witherspoon, Nashville; Jesse S. Myer, St. Louis; and Walter Bierring, Iowa City.

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Dr. Douglas Vanderhoof, Richmond, Va., read a paper on "Clinical Method for Determining the Sodium Chlorid Content of the Blood and Other Body Fluids." Discussed by Dr. Elliot P. Joslin, Boston, and Dr. Douglas Vanderhoof, Richmond, Va.

Dr. Harry Goodall and Dr. Elliot P. Joslin, Boston, presented a paper entitled, "Experiments on a Salt-Free Diet and Salt Metabolism, with Especial Reference to Diabetes Mellitus." Discussed by Drs. Alexander Lambert, New York; J. M. Allen, Liberty, Mo.; G. M. McCaskey, Fort Wayne, Ind., and Elliot P. Joslin, Boston.

Dr. R. H. Bellamy, Wilmington, N. C., read a paper on "An Epidemic of Pellagra." Discussed by Drs. William S. Thayer, Baltimore; John L. Dawson, Charleston, S. C.; Alfred Meyer, New York; and R. H. Bellamy, Wilmington, N. C.

Dr. Christopher Graham, Rochester, Minn., read a paper on "Gastric and Duodenal Ulcer." Discussed by Drs. W. J. Mayo, Rochester, Minn.; Fenton B. Turck, Chicago; J. M. Allen, Liberty, Mo.; Bertram W. Sippy, Chicago; Elliot P. Joslin, Boston; G. W. McCaskey, Fort Wayne, Ind.; Judson Daland, Philadelphia; M. Milton Portis, Chicago; and Christopher Graham, Rochester, Minn.

Thursday, June 4—Afternoon.

Dr. Heinrich Stern, New York, read a paper entitled, "Researches Concerning Compensatory Diarrheas." Discussed by Dr. George N. Jack, Buffalo.

Dr. Edward F. Wells, Chicago, said that the committee appointed desired to make a preliminary report and, in the absence of the chairman of that committee, Dr. Dock, he would present it. It was as follows:

Your committee, in presenting this preliminary report, is of the opinion that a fair presentation of conclusions and recommendations of the subject of program methods which you have delegated to it would require much prolonged consideration that a full report should be presented to the Section at its session next year; meanwhile your indulgence and assistance are asked. At this time, however, the committee will make some suggestions which are thought useful to the Section officers for their consideration in preparing the program for the ensuing year. These are, broadly, as follows:

At the discretion of the Section officers there should be included in the program the following classes of papers:

A. A series of symposiums, each consisting of not more than three papers, the presentation of which shall be limited to not more than twenty minutes each, with discussions limited to not more than ten minutes for the first, and five minutes for each subsequent speaker.

B. A series of well-selected papers on highly important separate subjects, the presentation of which shall not exceed twenty minutes each, with discussion limited to ten minutes for the first, and five minutes for each subsequent speaker.

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C. A series of short papers, the presentation of each to be limited to ten minutes, with discussions limited to five minutes to each speaker.

D. A series of papers to be presented in full abstract, the reading of which shall not exceed five minutes, with discussion limited to five minutes for each speaker.

E. A series of highly scientific research papers, to be printed in full, and distributed to members on request, at least two weeks before the meeting, with written discussion, not exceeding four hundred words presented to the Secretary on the opening day's session, to which the author of the paper may have access, with an allowance of ten minutes for him to present his position and reply to the written criticisms filed.

The practical application of these suggestions is left to the untrammeled good judgment of the Section officers, offering the hearty cooperation of the committee, and requesting such cooperation on their part and on the part of the members of the Section, in the consideration of the entire problem, and in the formulating of conclusions for presentation at the next annual session.

In conclusion, it is the sense of the committee that while rules and regulations may aid in furnishing the work of the Section they can not supplant the personal attention, judgment and discretion of the Section officers, but that on them in their preparation and management of the program and the conduct of the section work will largely depend the successful session.

In this connection it is recommended that fully accredited members make use of their prerogative in rising to a point of order whenever time is trespassed on by members in the presentation of papers or in their discussions.

George Dock, Chairman.
Allen Jones,
Alexander Lambert,
Edward F. Wells, Secretary.

The report was adopted.

Dr. Ralph S. Lavenson, Philadelphia, read a paper on "Acute Hemorrhagic Necroses of the Suprarenal Bodies." Discussed by Drs. S. Marx White, Minneapolis, and Ralph S. Lavenson, Philadelphia.

Drs. S. Marx White and Chelsea C. Pratt, Minneapolis, presented a communication on "Trichiniasis, with Report of Nine Cases." Discussed by Drs. William S. Thayer, Baltimore; S. R. Pietrowicz, Chicago; Joseph L. Miller, Chicago; Alfred Meyer, New York; James B. Herrick, Chicago, and S. Marx White, Minneapolis.

Dr. Alfred Stengel, Philadelphia, read a paper on "Modifications of the Clinical Course of Typhoid Fever Under the Influence of Menstruation and the Successive Menstrual Epochs; Treatment." Discussed by Dr Philip Marvel, Atlantic City, and Dr. Scott P. Child, Kansas City.

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Dr. H. Bascom Weaver, Asheville, N. C., read a paper entitled, "Tuberculin Therapy; Its Indications and Practical Application in the Treatment of Tuberculosis." Discussed by Drs. Koessler, Chicago; William Litterer, Nashville, Tenn., and H. Bascom Weaver, Asheville, N. C.

FRIDAY, JUNE 5—MORNING.

On motion of Dr. Johnson, Chicago, the Secretary was instructed to thank the congregation of Sinai Temple for the meeting place furnished the Section.

Dr. L. W. Ladd, Cleveland, read a paper on "Serum Treatment of Meningitis."

Dr. Lewellys F. Barker, Baltimore, and Dr. Frank J. Sladen, Baltimore, presented a paper entitled, "Report of a Series of Cases of Meningitis."

These two papers were discussed by Drs. W. S. Chase, Akron, Ohio; Johnson, Chicago; Edward F. Wells, Chicago; Joseph Eichberg, Cincinnati; Koessler, Chicago; D. E. English, Millburn, N. J.; O. M. Gilbert, Boulder, Colo.; L. W. Ladd, Cleveland, and Frank J. Sladen, Baltimore.

Dr. Hugo A. Freund, Detroit, read a paper entitled, "Pathology, Diagnosis and Treatment of So-called Hodgkin's Disease." Discussed by Drs. George Dock, Ann Arbor; Walter Bierring, Iowa City; John M. Swan, Philadelphia; George Douglas Head, Minneapolis; Edson B. Fowler, Chicago, and Hugo A. Freund, Detroit.

Dr. J. W. Shankland and Dr. William Engelback, St. Louis, presented a paper on "The Diagnostic Value of the Cutaneous and Conjunctival Tuberculin Reaction." Discussed by Drs. Gerald Bertram Webb, Colorado Springs; Frank Smithies, Ann Arbor; H. Bascom Weaver, Asheville, N. C.; John M. Swan, Philadelphia; Frederick T. Lord, Boston; Hugo A. Freund, Detroit; S. Marx White, Minneapolis; George Douglas Head, Minneapolis, and William Engelback, St. Louis.

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